

VII. APPLIED ASPECTS OF CVS PHYSIOLOGY

(a) ***To describe the responses to changes in posture.***

(I) CVS response from supine to standing:

Circulatory effects of becoming upright:

- Circulation is a column of fluid subject to the effects of gravity → moving to an upright position adds hydrostatic pressure (2° to gravity) to dependent parts of the body

Note:

- Supine position → hydrostatic pressures in cerebral vessels, aortic root and foot vessels are equal (I.e. P_{ART} 100 mmHg and P_{VEN} 15 mmHg)
- When going to upright position → hydrostatic pressures in vessels of feet ↑ by 120 cmH₂O (or 85-90 mmHg (as 1 cmH₂O = 0.75 mmHg)) as the foot is 120 cm below level of the heart (I.e. P_{ART} 190 mmHg and P_{VEN} 100 mmHg in foot)

- The consequence of this is that the ↑ hydrostatic pressures in the lower extremities causes ↑ venous pooling of blood there (as veins are highly compliant) → this causes ↓ venous return to the heart and ↓ C.O. → ↓ BP

Compensatory mechanisms to counter circulatory effects of becoming upright:

There are immediate compensatory mechanisms that restore BP within seconds:

- (1) Arterial baroreceptor reflex (main)
 - o ↓ BP causes ↓ stretching of high-pressure baroreceptors in carotid sinus and aortic arch → ↓ firing to NTS along CN IX and X, respectively → removal of inhibition of medullary vasomotor centres → ↑ SNS outflow (and ↓ PNS outflow) which maintains BP by causing:
 - (i) ↑ HR and myocardial contractility → ↑ C.O.
 - (ii) Venoconstriction of venous (capacitance) vessels → ↑ VR to ↑ C.O.
 - (iii) Vasoconstriction of arteriolar (resistance) vessels → ↑ SVR
- (2) Muscle pump in lower limbs
 - o If a patient moves their lower limbs after standing, muscle contraction squeezes blood back to the heart and keeps venous pressure < 30 mmHg in feet → prevents significant venous pooling in lower limbs and promotes ↑ VR and ↑ C.O.
- (3) Venous valves of lower limbs
 - o Brakes up column of venous blood in lower limbs and promotes unidirectional blood flow back to the heart
- (4) Thoracic pump
 - o ↑ ventilation with standing causes ↑ -ve intrathoracic pressures → favours VR back to heart → ↑ C.O.

Important to note – There are conditions where these compensatory mechanisms would be incomplete and BP cannot be properly maintained:

- (i) Hot environment → exaggerates venous pooling 2° to heat-induced peripheral vasodilation
- (ii) Standing still → removes effect of “muscle pump in lower limbs”
- (iii) Elderly → baroreceptors, SNS response, autoregulatory systems (I.e. of cerebral vessels) are less responsive, less effective and slower
- (iv) Autonomic neuropathy (I.e. DM) → less effective and slower SNS response

(II) Effect on cerebral blood flow (CBF) from supine to standing:

Determinants of CBF:

$$CBF = \frac{CPP}{CVR}$$

$$CPP = MAP - CVP \text{ (or ICP)} \rightarrow \text{due to “Starling Resistor” mechanism}$$

Effect of going upright on CBF:

- Circulation is a column of fluid subject to the effects of gravity → moving to an upright position adds hydrostatic pressure (2° to gravity) to dependent parts of the body → this has two effects:
 - (1) ↑ hydrostatic pressures in lower extremities of the body causes ↑ venous pooling of blood there (as veins are highly compliant) → this causes ↓ VR to the heart and ↓ C.O. → ↓ BP (and MAP) → ↓ CPP (and CBF)

Note:

- Supine position → hydrostatic pressures in cerebral vessels, aortic root and foot vessels are equal (I.e. P_{ART} 100 mmHg and P_{VEN} 15 mmHg)
- When going to upright position → hydrostatic pressures in vessels of feet ↑ by 120 cmH₂O (or 85-90 mmHg (as 1 cmH₂O = 0.75 mmHg)) as foot is 120 cm below level of heart (I.e. P_{ART} 190 mmHg and P_{VEN} 100 mmHg in foot)

- (2) ↓ hydrostatic pressures in the brain as it is higher level than the heart → ↓ CPP (and CBF)

Note – Brain is higher than heart by 30 cm in standing position → so vascular pressures in brain are 30 cmH₂O (or 22 mmHg) lower than the pressures in aortic root (90 mmHg) or RA (2 mmHg) → thus, P_{ART} 68 mmHg and P_{VEN} -20 mmHg at brain

- The fall in CPP (and CBF) is partly offset by the implications of “Monroe-Kellie doctrine” (I.e. cranium is fixed volume containing brain, blood, CSF) of decreasing ICP when going upright → this is due to:
 - (i) ↑ drainage of venous blood into the right heart (due to “Siphoning effect”) → this minimises ↓ cerebral blood volume → ↓ ICP → minimises ↓ CPP and CBF
 - (ii) ↑ drainage of CSF from brain to spinal cord (as CSF also acts as a column of fluid subject to the effects of gravity) → this ↓ CSF volume in cranium → ↓ ICP → minimises ↓ CPP and CBF
- Despite this, CPP (and CBF) ↓ by 20% initially → risk of cerebral ischaemia

Compensatory mechanisms that maintain CBF when going upright:

There are immediate compensatory mechanisms that restore CPP (and CBF) within seconds to minimise the risk of cerebral ischaemia:

- (1) Global compensation:
 - BP (and MAP) is the main determinant of CPP (and CBF) → see immediate compensatory mechanisms that restore BP above (I.e. arterial BRR, muscle pump, thoracic pump, venous valves)
- (2) Local compensation:
 - (i) Metabolic autoregulation – ↓ CBF will cause ↓ PaO_2 (2° to ↑ O_2 extraction), ↑ $PaCO_2$, ↑ K^+ and ↑ adenosine (2° to ↑ accumulation) → result in ↓ CVR 2° to cerebral vasodilation → restore CBF
 - (ii) Pressure (myogenic) autoregulation – ↓ CPP with upright position causes ↓ stretching of cerebral arterioles → results in reflex vasodilation that ↓ CVR 2° to cerebral vasodilation → restore CBF

Important to note – Local cerebral compensatory mechanisms can compensate for Δ in CBF a/w Δ in CPP, provided MAP is b/t 60 and 160 mmHg

(b) *To account for the cardiovascular changes seen in haemorrhage and hypovolaemia.*

Effects of haemorrhage:

Haemorrhage causes ↓ blood volume → ↓ MSFP of circulation → ↓ venous return and C.O. → ↓ arterial BP → ↓ driving pressure required for tissue blood flow (esp heart and brain)

Compensatory mechanisms that maintain BP during haemorrhage:

Immediate response (rapid – within seconds) → aims to (i) minimise Δ in effective BV to maintain C.O and arterial BP, and (ii) redistribute C.O. to brain and heart:

- (1) Arterial baroreceptor reflex (BRR):
 - ↓ BP causes ↓ stretching of “high-pressure baroreceptors” in carotid sinus and aortic arch → ↓ firing to NTS along CN IX and X, respectively → removal of inhibition of medullary vasomotor centres → ↑ SNS outflow (and ↓ PNS outflow) which rapidly preserves BP (within seconds) by causing:
 - (i) ↑ HR and myocardial contractility → ↑ C.O.
 - (ii) Venoconstriction of venous (capacitance) vessels → ↑ VR to ↑ C.O.
 - (iii) Vasoconstriction of arteriolar (resistance) vessels → ↑ SVR
- (2) Humoral response:
 - These responses are slightly delayed (10 mins to 1 hr to respond completely) → they aim to restore BV, which ↑ MSFP and ↑ VR back to heart → ↑ C.O. and BP:
 - (i) ↓ BV reduces stretching and stimulation of “low-pressure baroreceptors” in RA and pulmonary veins → causes ↑ ADH secretion and ↓ ANF production → ↑ BV 2° to ↑ Na⁺ and H₂O retention
 - (ii) ↓ RBF 2° to SNS-mediated renal vasoconstriction and ↓ BP causes ↑ renin secretion from macula densa → activates RAAS → ↑ AII, aldosterone and ADH levels → ↑ BV 2° to ↑ Na⁺ and H₂O retention
 - (iii) Stimulation of thirst (by ADH and AII)
 - (iv) BRR-related SNS outflow causes ↑ cortisol and catecholamine release from adrenal gland
- (3) Redistribution of C.O. to brain and heart:
 - (i) SNS-induced peripheral vasoconstriction occurs in skeletal muscle, skin, GIT → shunts blood flow towards brain and heart
 - (ii) Renal blood flow is variable (depending on severity of blood loss) → normally “autoregulated” (I.e. assuming MAP is b/t 75-170 mmHg), BUT with severe ↓ BV, ↓ BP and SNS-mediated renal arteriolar vasoconstriction there can be ↓ RBF → ↓ urine output (and ↓ Na⁺/H₂O loss), and shunting of blood flow to heart and brain
 - (iii) Cerebral and coronary blood flow are maintained (providing MAP > 70 mmHg) due to “autoregulation” (I.e. metabolic and pressure autoregulation)
- (4) Mobilisation of blood reservoirs (Eg. cutaneous, pulmonary, hepatic) → by SNS-induced venoconstriction of these circulatory systems
- (5) Restlessness increases muscle activity in lower limbs → ↑ VR to heart → ↑ C.O.
- (6) Transfer of fluid from interstitial space into plasma
 - SNS-mediated pre-capillary vasoconstriction alters capillary “Starling forces” by ↓ capillary P_{HYDROSTATIC} → promotes fluid absorption from ISF compartment into intravascular fluid compartment (I.e. up to 1 L/hr can be transferred!)
 - Depending on extent of blood loss, this may take as 12-24 hrs to complete
- (7) “Ischaemic CNS response”
 - Occurs when BP < 50 mmHg → massive SNS outflow from ischaemic medulla in last attempt to maintain BP and CPP (and CBF)

Delayed response (slow – within days-weeks) → aims to restore (i) plasma volume, (ii) plasma proteins, and (iii) RBC

- (1) Plasma volume normalises by 12-72 hrs → note that this causes “Dilutional anaemia”

- (2) $\uparrow$ erythropoiesis $\rightarrow \uparrow$ EPO from renal tubular cells in response to dilutional anaemia and blood loss stimulates BM to produce RBC $\rightarrow$ RBC count restored by 4-8 weeks
- (3) Plasma protein is synthesised by liver by 3-6 days

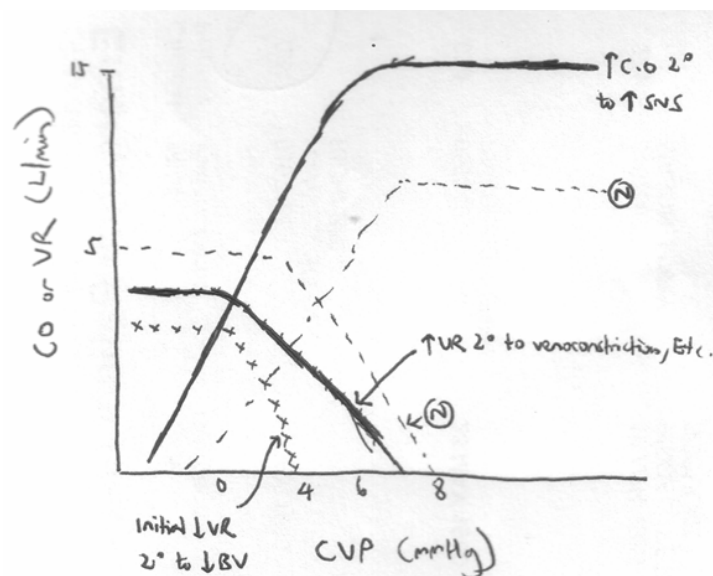
Important to note – These compensatory mechanisms are impaired in certain conditions, which predisposes to shock $\rightarrow$ this occurs with:

- (i) Elderly patients $\rightarrow$ due to impaired CVS responses (I.e. limited $\uparrow$ in C.O. or neurohumoral response)
- (ii) Other decompensating processes (esp lactic acidosis, hypothermia, arrhythmias, acute heart failure, Etc.) $\rightarrow$ further depresses CVS responses and tissue function

Physiological effects of haemorrhage $\rightarrow$ depend on the (i) rate and (ii) degree of blood loss

Blood volume loss	Effects
< 10% (< 500 mL)	Well-tolerated as compensatory mechanisms are adequate in maintaining BP and C.O. $\rightarrow$ MAP tends to be normal, but pulse pressure tends to be $\uparrow$ b/c of $\uparrow$ HR, $\uparrow$ SVR and $\downarrow$ BV
> 20% (> 1 L)	Rapid $\downarrow$ in arterial BP and C.O. as compensatory mechanisms inadequate
> 30% (> 1.5 L)	Irreversible hypotension and $\downarrow$ C.O. as compensatory mechanisms are grossly inadequate $\rightarrow$ results in inadequate tissue perfusion, leading to lactic acidosis (2 $^{\circ}$ to $\uparrow$ anaerobic glycolysis) $\rightarrow$ causes myocardial depression and $\downarrow$ vascular responsiveness to catecholamines
> 35-45% (> 2 L)	Cardiac arrest

Note – Effect of haemorrhage and its compensatory mechanisms on venous return and cardiac output curves:



- Loss of blood volume decreases MSFP, which shifts venous return curve to left $\rightarrow$ BUT compensatory mechanisms (Eg. venoconstriction, mobilisation of blood reservoirs, muscle activity, reabsorption of ISF, humoral response, Etc.) partially restore MSFP and shifts curve back to right
- SNS-mediated vasoconstriction decreases slope of venous return curve
- $\uparrow$ HR and myocardial contractility 2 $^{\circ}$ to SNS outflow will shift C.O. curve upwards

(c) *To explain the cardiovascular effects and responses in different forms of shock.*

“Shock” → state of significant ↓ systemic tissue perfusion resulting in ↓ O₂ delivery to tissues

Mechanism of shock:

- Systemic tissue perfusion is determined by driving pressure of blood to the tissue (or systemic BP):

$$\text{MAP} = \text{C.O.} \times \text{SVR}$$

- All forms of shock is caused by ↓ systemic tissue perfusion due to ↓ tissue driving pressure (or systemic BP), → this can be the result of – (i) ↓ C.O. and/or (ii) ↓ SVR (although C.O. or SVR can be reflexly ↑ in shock if the other is disproportionately low)

Types of shock and their haemodynamic profiles:

(1) Hypovolaemic shock

- Shock occurs due to ↓ C.O. 2° to ↓ preload (or PCWP) a/w intravascular volume loss → SVR reflexly ↑ to compensate for ↓ C.O.
- Causes of ↓ IVV are – (i) Haemorrhage (Eg. GI bleed, AAA rupture, Etc.) or (ii) Fluid loss (Eg. 3rd spacing, vomiting, diarrhoea, burns, Etc.)

(2) Cardiogenic shock

- Shock occurs due to ↓ C.O. 2° to cardiac pump failure. → preload and SVR reflexly ↑ to compensate for ↓ C.O.
- Causes of cardiac pump failure are – (i) Cardiomyopathy (Eg. MI, dilated cardiomyopathy, myocardial stunning 2° to sepsis, ischaemia, prolonged CPB), (ii) Arrhythmias (Eg. VT/VT, bradyarrhythmias, AF), (iii) Mechanical (Eg. valvular defect, atrial myoxmas, Etc.), or (iv) Extracardiac (Eg. massive PE, tension PTX, pericardial tamponade, constrictive pericarditis)

(3) Distributive shock

- Shock occurs due to severely ↓ SVR 2° to profound peripheral vasodilation → C.O. reflexly ↑ to compensate for ↓ BP
- Causes of peripheral vasodilation are – (i) Septic shock/SIRS, (ii) Anaphylaxis and anaphylactoid reactions, (iii) Neurogenic shock (Eg. spinal injury), (iv) Endocrine shock (Eg. Addisonian crisis, myxoedema coma)

Type of shock	PCWP (= preload)	C.O. (= pump function)	SVR (= afterload)	SvO ₂ (= tissue perfusion)
Hypovolaemic	↓	↓	↑	↓
Cardiogenic	↑	↓	↑	↓
Distributive	↓ or ↔	↑	↓	↑

Pathophysiology of shock → there are 4 stages:

(1) Initial stage

- Hypoperfusion and ↓ O₂ delivery to tissues leads to tissue hypoxia 2° to an imbalance b/t O₂ delivery and consumption → leads to ↑ cellular anaerobic metabolism and generation of lactate → metabolic lactic acidosis

(2) Compensatory stage

- Various mechanism aim to restore tissue perfusion (by ↑ BP) and counteract the sequelae of tissue hypoperfusion:
 - o (i) Peripheral chemoreceptors sense ↓ pH and ↓ pO₂ → causes ↑ ventilation to remove CO₂ to counter metabolic (lactic) acidosis

- (ii) High-pressure baroreceptors sense ↓ BP → cause ↑ SNS outflow to restore BP by ↑ HR, ↑ myocardial contractility, ↑ venoconstriction and ↑ vasoconstriction
- (iii) Low-pressure baroreceptors sense ↓ BP → cause activation of RAAS and ADH to restore BP by ↑ Na⁺/H₂O retention and ↑ vasoconstriction
- (iv) Diversion of blood flow from kidneys, GIT, skin, muscle to heart and brain (due to SNS-, ADH-, AII-mediated vasoconstriction of specific vascular beds)

(3) Progressive stage

- If shock is not adequately reversed, prolonged tissue hypoxia occurs → causes:
 - (i) Cellular effects – Irreversible cell damage occurs due to persistent anaerobic metabolism → cell membrane ion pump dysfunction occurs 2° to ↓ energy production (causes cellular oedema and lysis) and IC acidosis 2° to ↑ lactate production (impairs vital cellular enzymatic/metabolic function)
 - (ii) Systemic effects – Irreversible end-organ damage occurs due to metabolic (lactic) acidosis, prolonged organ hypoperfusion 2° to peripheral vasoconstriction, tissue oedema 2° to endothelial dysfunction, sludging of microcirculation 2° to ↑ blood viscosity, and activation of inflammatory cascades
- These effects cause shock to become irreversible as they impair above compensatory mechanisms from restoring tissue perfusion

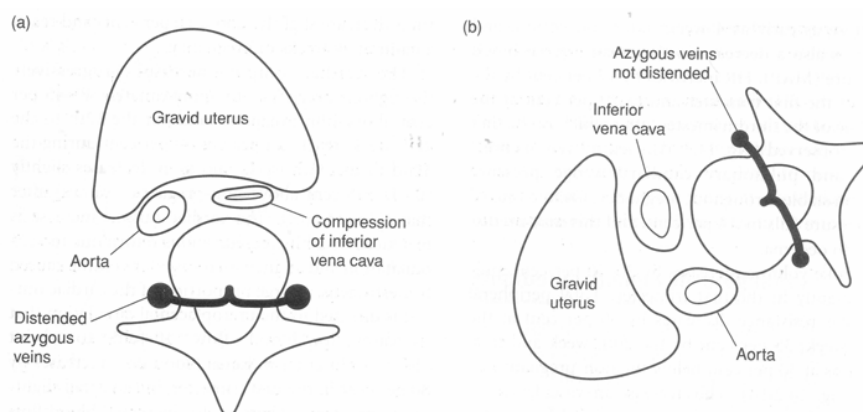
(4) Refractory stage

- Shock becomes irreversible and refractory to compensatory mechanisms → irreversible cell death, end-organ damage and multi-organ failure occur → death

(d) *To explain the cardiovascular responses in pregnancy, exercise, cardiac failure, and during intermittent positive pressure ventilation, anaesthesia, positive end-expiratory pressure, and the Valsalva manoeuvre.*

(I) CVS responses to pregnancy:

- (1) ↑ HR (by 15% at end of 1st TM → then by 25% by mid 3rd TM)
- (2) ↑ SV (by 20-30% from 8/40 to 32/40) → due to ↑ BV (40%)
- (3) ↑ C.O. (by 30% from 8/40 to 32/40) → due to ↑ HR, ↑ SV (a/w ↑ BV), ↓ TPR (a/w ↑ VR), and ↑ MRO₂
- (4) ↓ SVR (by 20-30% by end of 1st TM) → due to (i) placental circulation (10% of C.O.) acting as a low resistance AV shunt, and (ii) progesterone and PG-mediated peripheral vasodilation (esp renal, splanchnic, heart, breasts, skin circulation)
- (5) ↓ PVR (by 35% by end of 1st TM) → due to progesterone/prostaglandins
- (6) ↑ tissue blood flow (esp to uterus/placenta, heart, kidneys, GIT, breasts, skin) → due to (i) ↑ C.O. and (ii) hormone-mediated regional vasodilation – Nb. CBF is NOT affected!!!
- (7) ↓ BP (↓ MAP, ↓ DBP > ↓ SBP) by 10% (esp at 20/40) due to ↓ SVR → BUT this normalizes towards term
- (8) CVP and PCWP unchanged
- (9) Aortocaval compression
 - Abdominal aorta and IVC may be occluded by effects of gravid uterus as early as 2nd TM (max. effect at 36-38/40), especially when supine → characterised by:
 - (i) Complete compression of IVC:
 - 85% of ♀ – Compensatory vasoconstriction, tachycardia and collateral blood flow (venous return diverted via paravertebral and epidural veins into azygous system → SVC) maintains VR/C.O. and MAP
 - 15% of ♀ – “Supine hypotension syndrome” occurs as compensatory mechanisms are insufficient → results in ↓ VR/C.O. and MAP → causes hypotension, bradycardia, pallor, syncope, N/V, sweating
 - (ii) Partial compression of abdominal aorta → causes ↓ uteroplacental BF by 20% (causing foetal distress) and ↓ renal BF
 - This is prevented by positioning mother on left side



Note – During labour:

- (i) C.O. – ↑ 15% (early labour), ↑ 30% (1st stage), ↑ 45% (2nd stage), ↑ 65% (post-partum), then normalizes 2/52 post-partum
- (ii) Uterine contractions and uterine involution post-partum squeezes 300 mL of blood out of uterus into circulation (“Autotransfusion”) causes ↑ VR → ↑ SV/C.O.
- (iii) BP – ↑ 10-20 mmHg with uterine contractions. Normalises 2/52 post-partum
- (iv) CVP ↑ (4-6 cmH₂O) due to ↑ VR a/w autotransfusion

(II) CVS responses to exercise:

Exercise is a/w extensive changes in CVS to meet the $\uparrow$ needs of O_2 /nutrient supply and removal of CO_2 , heat and metabolites from the body

The main CVS response to exercise is to $\uparrow$ blood flow to “working tissues” (Eg. skeletal muscle, heart, skin), while redistributing blood flow away from “non-working tissue” (Eg. GIT, kidneys):

- (1) $\uparrow$ skeletal muscle blood flow $\rightarrow$ to $\uparrow$ O_2 /nutrient delivery to meet the $\uparrow$ demands a/w energy (Eg. ATP) generation required for muscle contraction:
 - o Skeletal muscle receives 20% of C.O. (1 L/min) at rest $\rightarrow$ this $\uparrow$ to 80-90% of C.O. (20-30 L/min) with severe exercise
 - o This is due to:
 - (i) Local factors – $\uparrow$ muscle metabolism causes $\uparrow$ K^+ , ADP, H^+ , CO_2 , and temperature $\rightarrow$ causes local vasodilation
 - (ii) Systemic factors – $\uparrow$ C.O. and $\uparrow$ systemic BP

Note – During muscle contraction, intramuscular pressure $\uparrow$ $\rightarrow$ impedes muscle blood flow. This is important as there are two types of exercise:

- (a) Isotonic (dynamic) exercise – Usual form of exercise where muscle length changes $\rightarrow$ blood flow occurs during relaxation b/t muscle contraction
- (b) Isometric (static) exercise – Muscle length remains constant $\rightarrow$ continuous muscle contraction causes significant $\downarrow$ blood flow

Note – O_2 extraction can also be $\uparrow$ to satisfy $\uparrow$ O_2 demands $\rightarrow$ OHDC is shifted to the right due to $\uparrow$ CO_2 and H^+ (Bohr effect), $\uparrow$ temperature and $\uparrow$ 2,3-DPG

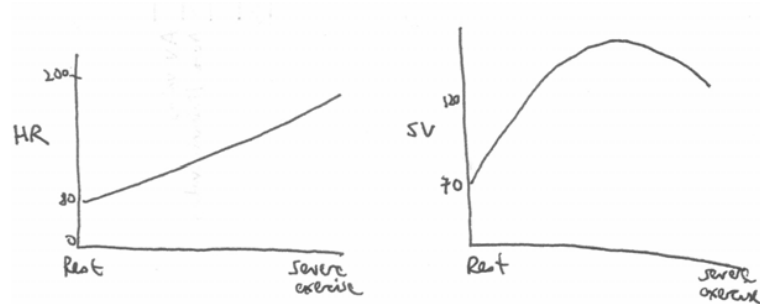
- (2) $\uparrow$ Coronary blood flow $\rightarrow$ to $\uparrow$ O_2 /nutrient delivery to meet $\uparrow$ demands of $\uparrow$ C.O.:
 - o CorBF is 250 mL/min at rest, but can $\uparrow$ to 1000 mL/min with severe exercise
 - o This is due to vasodilation 2° to local mechanisms or effects of circulating catecholamines on β_2 receptors in coronary vessels
- (3) $\uparrow$ skin blood flow $\rightarrow$ to dissipate heat
- (4) $\downarrow$ renal and splanchnic blood flow (due to $\uparrow$ SNS-induced vasoconstriction) $\rightarrow$ redistributes blood flow to skeletal muscle, heart and skin

Important to note – Cerebral blood flow is UNCHANGED (750 mL/min)

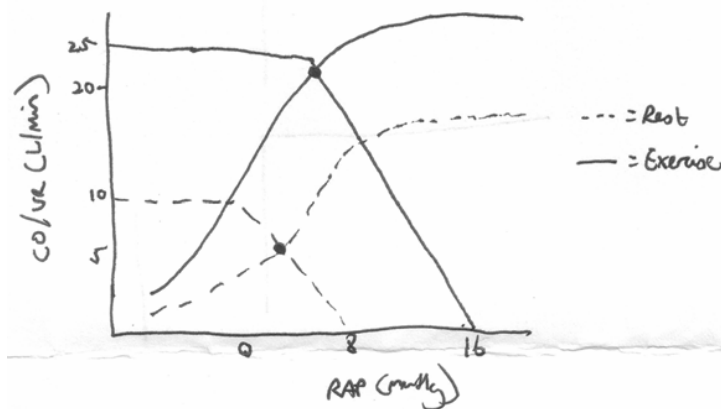
C.O. $\uparrow$ by 5X with exercise (from 5 L/min at rest, up to 20-30 L/min with severe exercise) $\rightarrow$ this is due to:

- (1) Muscle pump – Cyclic contraction of limb muscles cause intermittent compression of deep veins contract $\rightarrow$ facilitates venous return of blood to the heart (provided venous valves are competent)
- (2) Thoracic pump – During inspiration, intrathoracic pressure $\downarrow$ and intra-abdominal pressure $\uparrow$ $\rightarrow$ this compresses abdominal veins $\rightarrow$ facilitates VR back to heart (Nb. this is enhanced with $\uparrow$ depth and frequency of breathing)
- (3) SNS-mediated peripheral venoconstriction $\rightarrow$ $\downarrow$ venous capacitance, which $\uparrow$ VR back to heart
- (4) SNS-mediated peripheral vasoconstriction (esp splanchnic and renal circulation) $\rightarrow$ diverts blood flow to skeletal muscles, which then $\uparrow$ VR back to heart
- (5) Vasodilation of skeletal muscle vasculature due to local mechanisms (Ie. metabolites) $\rightarrow$ causes $\downarrow$ afterload 2° to $\downarrow$ SVR (EXCEPT during isometric (static) exercise, where afterload and SVR $\uparrow$ due to continuous compression of muscle vasculature)
- (6) $\uparrow$ HR and contractility

- $\uparrow$ C.O. is mainly due to $\uparrow$ HR $\rightarrow$ HR $\uparrow$ linearly (by 2-3x) with exercise up to a peak of 180-200 bpm $\rightarrow$ due to initial $\downarrow$ PNS (vagal) activity, followed by $\uparrow$ SNS activity
- SV can $\uparrow$ only 10-35% $\rightarrow$ SV $\uparrow$ non-linearly with exercise (mostly during light-moderate exercise; small $\uparrow$ with heavy exercise) $\rightarrow$ due to $\uparrow$ EDV (2° to $\uparrow$ VR to heart) and $\downarrow$ ESV (2° to $\uparrow$ emptying with $\uparrow$ SNS activity)



Effects on C.O. and VR curves:

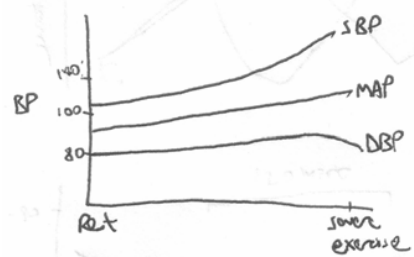


Note:

- $\uparrow$ C.O. due to $\uparrow$ HR/contractility
- $\uparrow$ MSFP due to $\uparrow$ VR from muscle pump, thoracic pump, and venoconstriction
- $\uparrow$ slope of VR curve due to $\downarrow$ resistance to venous return

Effects of exercise on BP is variable:

- (1) $\uparrow$ SBP and MAP (due to $\uparrow$ C.O.) $\rightarrow$ vital in providing driving pressure for blood flow to skeletal muscle, heart and skin
- (2) DBP unchanged, $\uparrow$ slightly, or $\downarrow$ (due to $\downarrow$ SVR a/w vasodilation in skeletal muscle)
- (3) Pulse pressure $\uparrow$ (by 2-3x)



Note – “Baroreceptor reflex” is set to a higher set-point with severe exercise to accommodate a $\uparrow$ in SBP and MAP

Of note, the CVS responses to exercise vary with the types of exercise:

- (a) Isometric (static) exercise $\rightarrow$ $\uparrow$ HR, $\uparrow$ BP (SBP, DBP and MAP) and $\uparrow$ C.O. $\rightarrow$ BUT b/c of continuous muscle contraction, the $\uparrow$ SVR and afterload causes (i) the $\uparrow$ in BP to be greater than the $\uparrow$ in C.O., and (ii) DBP to $\uparrow$ also
- (b) Isotonic (dynamic) exercise $\rightarrow$ $\uparrow$ HR, $\uparrow$ BP (SBP and MAP only) and $\uparrow$ C.O. $\rightarrow$ BUT b/c of intermittent muscle relaxation, the $\downarrow$ SVR and afterload causes (i) $\downarrow$ DBP (which causes a $\downarrow$ rise in MAP), (ii) $\uparrow$ rise in HR (in response to $\downarrow$ rise in MAP), (iii) $\uparrow$ rise in C.O.

(III) CVS responses to cardiac failure:

“Heart failure” → inability of the heart to pump a sufficient amount of blood to meet the metabolic demands of the body

Heart failure can be classified various ways:

- (1) Systolic vs diastolic dysfunction:
 - (a) Systolic dysfunction → caused by:
 - (i) Impaired contractility (Eg. myocardial dysfunction 2° to CAD, valvular disease, arrhythmias, dilated cardiomyopathy, Etc.)
 - (ii) ↑ afterload (Eg. HTN, AS, Etc.)
 - (b) Diastolic dysfunction → caused by:
 - (i) Impaired ventricular relaxation → due to impaired diastolic relaxation (Eg. myocardial ischaemia 2° to CAD) or ↑ ventricular wall stiffness (Eg. LVH 2° to HTN, hypertrophic or restrictive cardiomyopathy)
 - (ii) Obstruction to ventricular filling (Eg. mitral stenosis, cardiac tamponade, pericardial disease)
- (2) Left vs right ventricular failure:
 - (a) LVF is more common → often a/w secondary RV involvement
 - (b) Isolated RVF can occur with advanced lung parenchyma or pulmonary vasculature disease
- (3) High vs low output failure:
 - (a) Low output failure (more common) → characterised by ↓ C.O. to the body as the pump action of heart is compromised (Eg. systolic and diastolic dysfunction)
 - (b) High output failure (less common) → characterised by ↑ C.O. BUT insufficient to satisfy the systemic metabolic demands of the body (Eg. sepsis, thyrotoxicosis, Beri-Beri, Etc.)

Clinical features of heart failure → caused by:

- (1) Inadequate O₂ delivery to tissues 2° to ↓ C.O. – ↓ MVB PO₂ and SO₂ and ↑ arteriovenous O₂ content difference (due to ↑ tissue extraction), metabolic acidosis, fatigue, O₂ debt
- (2) Backflow of blood behind failing ventricle – (i) Systemic venous congestion (for RVF) → peripheral oedema, hepatic congestion, ascites, or (ii) Pulmonary venous congestion (for LVF) → pulmonary oedema

Compensatory responses to heart failure:

Important to note – Compensatory responses to heart failure can initially preserve C.O. (and BP) in mild-moderate cardiac dysfunction → BUT with increasing severity of cardiac dysfunction, these responses can further exacerbate cardiac dysfunction

(1) ↑ preload:

- Acutely volume- or pressure-overload ventricle produces ↑ wall stress → ventricles respond by dilating to ↑ preload (Ie. ↑ ventricular EDV and EDP) to maximise stroke volume by moving up “Frank-Starling” curve to restore C.O. (despite ↓ ejection fraction)
- Mechanism – Lengthening of sarcomeres 2° to ventricular dilatation optimises actin-myosin overlapping → results in ↑ myocardial contractility

Limitations of ↑ preload:

- (i) Worsening of venous congestion due to backflow from failing ventricle (Ie. pulmonary or systemic venous congestion)
- (ii) Excessive ventricular dilation stretches the AV valve annulus → causes valvular regurgitation that further impairs ventricular output
- (iii) C.O. ↑ slightly only with ↑ preload at the “plateau” phase of C.O. curve

(2) Activation of neurohormonal responses:

- (a) ↑ SNS activation
 - Baroreceptors sense ↓ BP (2° to ↓ C.O.) with heart failure → inhibits arterial BRR, causing ↑ SNS outflow (and ↓ PNS outflow) to maintain BP (and C.O.) by:
 - (i) ↑ HR and myocardial contractility to ↑ C.O.
 - (ii) Venoconstriction of capacitance vessels to ↑ VR back to heart
 - (iii) Vasoconstriction of resistance vessels in specific vascular beds (GIT, kidneys, skeletal muscle and skin only) to ↑ SVR and redistribute blood flow to heart and brain
- (b) ↑ RAAS response
 - ↓ renal perfusion and ↑ SNS-mediated β1-adrenergic activity of JGA causes ↑ renin release and activates RAAS response → leads to ↑ AII and ↑ aldosterone
 - This causes – (i) ↑ Na⁺/H₂O retention and thirst → ↑ intravascular volume and ↑ preload, which ↑ ventricular output 2° to Frank-Starling mechanism, (ii) peripheral vasoconstriction → ↑ SVR and BP, and (iii) ↑ ADH release (see below)
- (c) ↑ ADH release
 - ADH is secreted from posterior pituitary in response to AII and activation of low-pressure baroreceptors in heart/great vessels
 - This causes – (i) ↑ H₂O retention and thirst → ↑ intravascular volume and ↑ preload, which ↑ ventricular output 2° to Frank-Starling mechanism, (ii) peripheral vasoconstriction → ↑ SVR and BP
- (d) ↑ ANP release
 - ANP is secreted by atrial cells in response to distension → inhibits release of AII, aldosterone, and ADH (I.e. Na⁺/H₂O excretion) and causes vasodilation

Limitations of neurohormonal responses:

- (i) Vasoconstriction of resistance vessels (2° to ↑ SNS activity, ADH and AII) causes ↑ afterload → impairs C.O.
- (ii) SNS-mediated +ve ino- and chronotropy → ↑ metabolic O₂ demand of heart
- (iii) Chronic SNS activation causes “downregulation” of adrenergic receptor response to catecholamines → causes heart to be dependent on catecholamines such that abrupt withdrawal in SNS output (Eg. GA) can cause acute decompensation
- (iv) ↑ intravascular volume (2° to ADH, AII, aldosterone) worsens venous congestion due to backflow from failing ventricle

(3) Ventricular hypertrophy:

- Chronic ↑ ventricular wall stress leads to compensatory ↑ ventricular muscle mass and hypertrophy → counters wall stress and maintains myocardial contractility
- There are 2 types of ventricular hypertrophy:
 - (a) Eccentric hypertrophy
 - Chronic volume overloaded ventricle creates ↑ diastolic wall stress and ventricular dilatation → this is countered by ↑ ventricular wall thickness in proportion to ventricular diameter (I.e. sarcomeres replicate in series) → this maintains myocardial contractility at ↑ preload (or ↑ ventricular EDV/EDP) to maintain SV and C.O.
 - (b) Concentric hypertrophy
 - Chronic pressure overloaded ventricle creates ↑ systolic wall stress and ventricular dilatation → this is countered by ↑ ventricular wall thickness in excess of ventricular diameter (I.e. sarcomeres replicate in parallel) → this ↓ afterload (as per Law of LaPlace), which ↓ ventricular ESV and maintains SV and C.O.

Limitations of ventricular hypertrophy → ↑ diastolic dysfunction 2° to ↓ ventricular compliance (I.e. need ↑ EDV/EDP to maintain SV)

(IV) CVS responses during IPPV and PEEP:

Overview of IPPV:

- Use of +ve intrathoracic pressures to ventilate lungs (cf. -ve intrathoracic pressures with normal breathing) → Nb. there is reversal of pleural and alveolar pressures b/t IPPV and normal breathing
- Consists of 2 phases:
 - o (i) Inspiratory phase → +ve pressure is given through an airway from a ventilator to produce a given tidal volume
 - o (ii) Expiratory phase → +ve pressure is released as the lungs deflate passively

Cardiac effects of IPPV:

During inspiration → there is ↑ intrathoracic pressure (ITP) → causes following effects:

- (1) Initially, there is ↑ LV stroke volume and output due to ↑ LV preload → due to “squeezing” of blood from pulmonary circulation to the LA then LV as a result of ↑ ITP
- (2) Later, there is ↓ LV stroke volume and output due to ↓ LV preload → due to:
 - o (i) ↓ venous return to the right heart → b/c ↑ ITP increases RA pressures, thus effectively ↓ the pressure gradient favouring systemic venous return to the RA
 - o (ii) ↓ venous return to the left heart → b/c of ↓ RV output caused by ↑ RV afterload 2° to ↓ pulmonary vascular compliance and ↑ pulmonary vascular resistance brought on by ↑ ITP
 - o (iii) Effects of “ventricular interdependence” → ↑ RV chamber size (caused by ↑ RVESV 2° to ↑ RV afterload) pushes the interventricular septum to the left, thus ↓ chamber volume of LV for a given filling pressure
 - o (iv) “External splinting” → ↑ ITP reduces LV compliance to LV chamber filling
- (3) LV afterload ↓ (and thereby facilitating LV output) due to:
 - o (i) ↑ pressure gradient from thorax to abdomen
 - o (ii) ↓ transmural gradient → ↓ LV wall tension (as a result of “Law of LaPlace”, whereby wall tension is proportional to transmural pressure)

During expiration → there is ↓ ITP → causes the following effects:

- (1) Initially, there is ↓ LV stroke volume and output due to ↓ LV preload → due to sudden expansion of pulmonary vessels (I.e. ↑ pulmonary vascular capacitance and ↓ pulmonary vascular resistance 2° to ↓ ITP), which ↓ venous return to left side of heart
- (2) Later, LV preload, stroke volume and output return to pre-inspiratory levels as:
 - o (i) Venous return to the right heart resumes (as RAP normalises with ↓ ITP)
 - o (ii) Venous return to the left heart resumes (as RV afterload decreases with ↓ ITP) → permits blood from right heart to flow through pulmonary vessels into left heart

Effects of IPPV on LV output → highly variable:

- Normal LV function – IPPV causes ↓ LV output (I.e. ↓ C.O. and BP) b/c of ↓ LV preload
- Impaired LV function (Eg. CCF) or elderly – IPPV preserves or ↑ LV output (I.e. C.O. and BP unchanged or ↑) b/c of ↓ LV preload and ↓ LV afterload

Note – Thus, IPPV is beneficial in patients with ↓ LV function!

Important to note – Hypovolaemia, PEEP and high mean airway pressure exaggerate the fall in LV output (and C.O. and BP) with IPPV → this is b/c:

- Hypovolaemia is a/w ↓ CVP → thus, ↓ ability to offset the fall in venous return a/w IPPV
- PEEP/high mean airway pressures is a/w ↑ inspiratory pressures and ITP → thus, further effects on ↓ LV preload a/w IPPV

Other effects of IPPV:

- (i) ↓ RBF, ↓ GFR and U/O → due to ↓ C.O. and ↑ CVP

- (ii) ↑ ADH and AII levels
- (iii) ↓ HBF → due to ↓ C.O. and ↑ CVP
- (iv) ↑ ICP → due to ↑ CVP and ↓ venous return

Overview of PEEP:

- PEEP is +ve airway pressure at end-expiration → it is used to offset falls in FRC (a/w ↓ lung compliance, ↑ V/Q mismatching (esp shunting) and ↓ PaO₂) in patients who are spontaneously breathing or being mechanically ventilated

Cardiac effects of PEEP:

PEEP can ↓ C.O. due to ↑ intrathoracic pressures → causes ↓ LV SV (or preload) and output due to:

- (1) ↓ venous return to right heart → b/c ↑ ITP increases RA pressures, thus effectively ↓ the pressure gradient favouring systemic venous return to the RA
- (2) ↓ venous return to left heart → b/c of ↓ RV output caused by ↑ RV afterload 2° to ↓ pulmonary vascular compliance and ↑ pulmonary vascular resistance brought on by ↑ ITP
- (3) Effects of “ventricular interdependence” → ↑ RV chamber size (caused by ↑ RVESV 2° to ↑ RV afterload) pushes the interventricular septum to the left, thus ↓ chamber volume of LV for a given filling pressure
- (4) “External splinting” → ↑ ITP reduces LV compliance to LV chamber filling

Effect of PEEP on LV output → highly variable:

- Moderate levels of PEEP (< 15 cmH₂O) in patients with normal LV function have little impact on C.O. → of note, any ↓ C.O. can be negated by intravascular volume loading
- PEEP may ↑ C.O. in patients with poor LV function (Ie. elderly and CCF) due to:
 - (1) ↓ LV afterload due to – (i) ↑ pressure gradient from thorax to abdomen, and (ii) ↓ transmural gradient → ↓ LV wall tension (as a result of “Law of LaPlace”, whereby wall tension is proportional to transmural pressure)
 - (2) ↓ LV preload (due to above factors)

Important to note – Hypovolaemia, excessive PEEP (esp > 15 cmH₂O) and IPPV (esp high mean AW pressures) → exaggerate fall in LV output (and C.O. and BP) with PEEP → this can be offset by adequate intravascular volume loading

Other effects of PEEP:

- (i) ↓ RBF, ↓ GFR and U/O → due to ↓ C.O. and ↑ CVP
- (ii) ↑ ADH and AII levels
- (iii) ↓ HBF → due to ↓ C.O. and ↑ CVP
- (iv) ↑ ICP → due to ↑ CVP and ↓ venous return

(V) CVS responses to anaesthesia:

CVS responses to volatile agents:

- (i) HR – Some blunt BRR/SNS response (sevoflurane, halothane) and cause ↓ HR or no changes in HR. Some retain BRR/SNS response (desflurane, isoflurane) and cause reflex ↑ HR 2° to ↓ C.O./BP. Halothane is a/w junctional rhythm/bradycardia due to ↑ vagal tone and direct SAN/AVN depression
- (ii) C.O. – All volatiles depress myocardium and ↓ myocardial contraction (esp halothane), but intact BRR/SNS response (desflurane, isoflurane, N₂O) can maintain C.O. due to reflex ↑ HR. Those with blunted BRR/SNS response (sevoflurane, halothane) have ↓ C.O.
- (iii) BP – All volatiles have ↓ BP (most with halothane) due to ↓ SVR and/or ↓ C.O., except N₂O which has unchanged BP due to intact SNS response
- (iv) SVR – All agents ↓ SVR (except for halothane, which is unchanged)
- (v) PVR – All agents ↓ PVR due to impaired HPV (except N₂O, which ↑ PVR)
- (vi) Arrhythmogenic potential – All agents prolong QTc (risk of Torsades de Pointes), but halothane sensitises myocardium to arrhythmogenic effects of catecholamines (risk of VEB, VT, VF)
- (vii) Most agents (esp isoflurane, desflurane, sevoflurane) possess “ischaemic preconditioning”
- (viii) All agents ↓ myocardial O₂ demands but effects on coronary BF is variable

CVS responses to induction agents:

- (i) HR – STP causes ↑ HR (due to intact BRR/SNS output); Ketamine cause ↑ HR (due to direct central SNS outflow and inhibition of NAd reuptake centrally and peripherally); Propofol causes ↓ HR (due to blunted BRR/SNS output and ↑ vagal outflow); Etomidate has minimal change in HR (due to intact BRR/SNS output)
- (ii) C.O. – All agents are direct myocardial depressants, but change in C.O. is minimal for STP (and even less so for Etomidate) due to intact BRR/SNS output; Propofol causes ↓ C.O. (as BRR/SNS output is blunted); Ketamine causes ↑ C.O. due to indirect SNS effects
- (iii) BP – All agents cause ↓ BP, although it is mild with STP and Etomidate; Propofol causes significant ↓ BP; Ketamine causes ↑ BP
- (iv) SVR – All agents cause ↓ SVR due to peripheral vasodilation; SVR is unchanged with ketamine
- (v) Myocardial O₂ balance – STP and ketamine ↑ MRO₂ and CBF; Propofol has the opposite effect; Etomidate MRO₂/CBF is stable

CVS responses to opioids:

- (i) HR – All opioids cause ↓ HR → due to ↑ CN X (vagal) nuclei output, blunting of BRR and direct depression of SAN/AVN (EXCEPT pethidine which ↑ HR due to anticholinergic effect)
- (ii) C.O. – All opioids can ↓ C.O. due to ↓ HR and blunted BRR (however, they have no direct myocardial depressive effects)
- (iii) BP – All opioids can ↓ BP due to ↓ C.O. and blunted BRR (but especially morphine and pethidine due to peripheral vasodilation 2° to histamine release)

CVS responses to local anaesthetics:

- LAs depress conduction of cardiac impulse → can be therapeutic (Eg. treat ventricular arrhythmias)
- BUT at toxic levels (Ie. accidental IVI) can cause transient CVS excitation initially (Eg. ↑ HR and BP), but later CVS depression (Eg. bradycardia, AVHB, profound hypotension, cardiac arrest)

(VI) CVS responses to Valsalva manoeuvre:

“Valsalva manoeuvre” → forced expiration against a closed airway – closed mouth and nose (or closed glottis) – to 50 cmH₂O (or 40 mmHg) for 10-15 secs → a/w ↑ intrathoracic pressure, ↑ intrabdominal pressure, ↑ central venous pressure, ↑ CSF pressure, and ↑ ICP

Note – It is performed by blowing into a mercury column to produce a pressure of 50 cmH₂O (or 40 mmHg) and holding it for 10-15 sec

CVS changes associated with Valsalva manoeuvre:

Valsalva manoeuvre produces a characteristic circulatory response to Δ s in intrathoracic pressure → divided into 4 phases:

Note: Phase I and II → ↑ intrathoracic pressure due to straining
Phase III and IV → intrathoracic pressure normalises due to relief of straining

Phase I

- Onset of straining → causes a transient and small ↑ in BP a/w a brief ↓ in HR
- This is due to a sudden ↑ in ITP → causes (i) compression of intra-pulmonary vessels, which promotes ↑ VR to left heart and ↑ LV SV, and (ii) transmission of ↑ ITP onto aorta

Phase II

- With continued straining → ↑ ITP causes ↓ VR to right heart → causes ↓ C.O. and ↓ BP
- This is sensed by arterial BRR, which produces ↑ SNS outflow (and ↓ PNS outflow) → causes ↑ HR and peripheral vasoconstriction → attenuates any further ↓ in BP

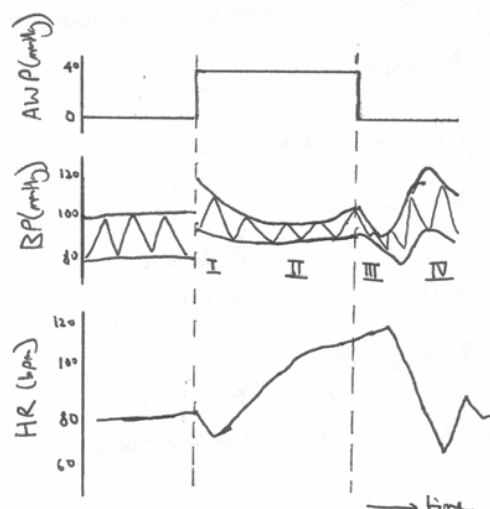
Note – Pulse pressure is ↓ b/c of – (i) ↓ C.O. (lowers SBP), and (ii) peripheral vasoconstriction (keeps DBP ↑)

Phase III

- Relief of straining causes ITP to ↓ rapidly → causes ↓ in BP a/w further ↑ in HR
- This is due to sudden ↓ in ITP → causes (i) ↓ compression of intra-pulmonary vessels, which ↓ VR to left heart and ↓ LV SV, and (ii) loss of transmitted ↑ ITP onto aorta

Phase IV

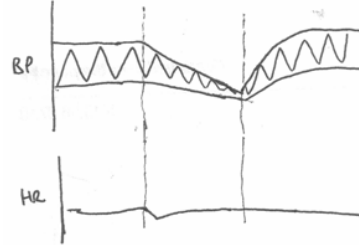
- ITP returns back to baseline → causes VR to left heart normalise, which restores C.O. → BUT peripheral vasoconstriction persists, causing an overshoot of ↑ BP
- This stimulates arterial BRR to produce ↓ SNS outflow (and ↑ PNS outflow) → causes reflex bradycardia and peripheral vascular relaxation → later restores BP back to normal



Abnormal responses to Valsalva manoeuvre:

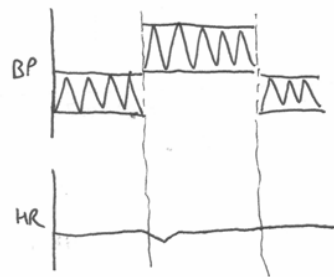
(1) Diminished arterial BRR (Eg. DM autonomic neuropathy, quadriplegia)

- Excessive $\downarrow$ BP and lack of $\uparrow$ HR during Phase II $\rightarrow$ due to absence of BRR-mediated $\uparrow$ HR and peripheral vasoconstriction
- Absence of overshoot in BP and bradycardia in Phase IV $\rightarrow$ b/c C.O. is restored in an absence of peripheral vasoconstriction, so BP normalises gradually



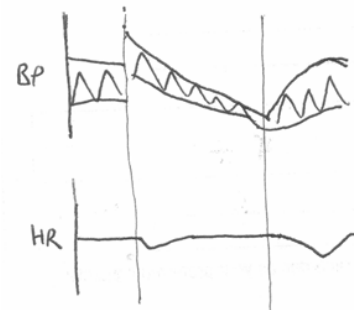
(2) Congestive heart failure $\rightarrow$ produce “square-wave response”:

- BP is $\uparrow$ during Phases I and II, and there is a lack of $\uparrow$ HR in Phase II $\rightarrow$ this is b/c CHF is a/w $\uparrow$ pulmonary blood volume $\rightarrow$ provides a blood reservoir that maintains LV filling following onset of straining and raised ITP $\rightarrow$ as C.O. and BP are preserved, arterial BRR is not activated
- BP normalises in Phases III and IV, and there is a lack of BP overshoot or $\downarrow$ HR in Phase IV $\rightarrow$ this is b/c BRR-mediated vasoconstriction is absent in Phase II



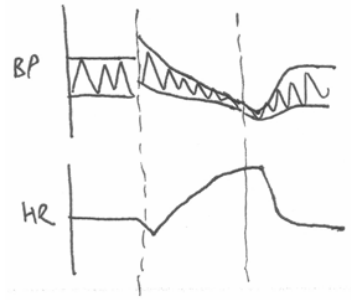
(3) β -adrenergic blockade

- Excessive $\downarrow$ BP and lack of $\uparrow$ HR during Phase II $\rightarrow$ due to β -blockade of BRR-mediated $\uparrow$ in HR
- Smaller overshoot in BP and fall in HR in Phase IV $\rightarrow$ despite intact BRR-mediated vasoconstriction, C.O. and BP does not rapidly $\uparrow$ due to lack of $\uparrow$ HR in Phase II



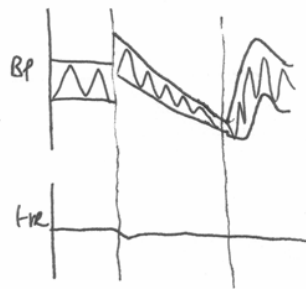
(4) α -adrenergic blockade (= neuraxial block)

- Excessive $\downarrow$ BP and $\uparrow$ HR during Phase II $\rightarrow$ due to loss of reflex peripheral vasoconstriction in the context of a vigorous arterial BRR response to $\downarrow$ BP
- Absence of overshoot in BP and bradycardia in Phase IV $\rightarrow$ due to lack of BRR-mediated peripheral vasoconstriction in the context of a restored C.O.



(5) Heart transplant (or denervated heart → no β - or vagal innervation):

- Exaggerated $\downarrow$ BP and lack of $\uparrow$ HR in Phase II → due to lack of β -mediated $\uparrow$ HR following reflex inhibition of arterial BRR
- Overshoot in BP in Phase IV but not a/w $\downarrow$ in HR → restoration of C.O. in context of intact peripheral vasoconstriction causes $\uparrow\uparrow\uparrow$ BP, but stimulation of arterial BRR cannot produce vagal-mediated $\downarrow$ HR



Uses of Valsalva manoeuvre:

- (1) Clinical assessment of ANS function → determined by calculating “Valsalva Ratio”, which evaluates the compensatory HR responses as a result of arterial BRR response to Δ s in BP during Valsalva manoeuvre

$$VR = \frac{\text{Maximum HR in Phase II}}{\text{Minimum HR in Phase IV}} = \frac{\text{Longest R-R interval in Phase IV}}{\text{Shortest R-R interval in Phase II}}$$

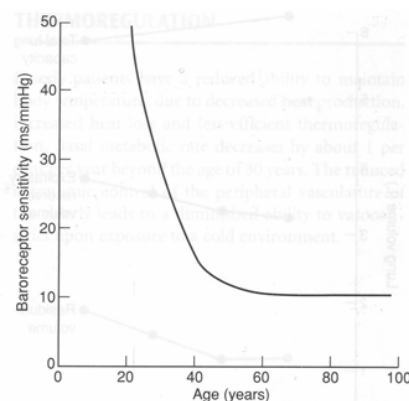
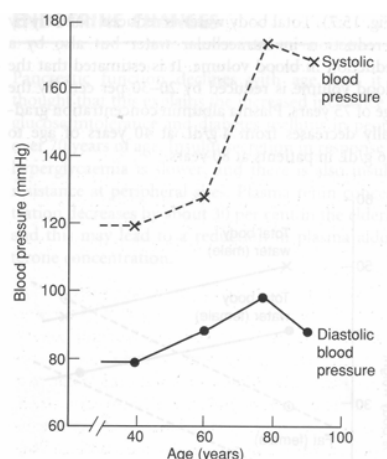
VR is normally > 1.5 → BUT it is < 1.5 with impaired ANS function or arterial BRR function (I.e. elderly, DM neuropathy, Etc.)

- (2) Slow or terminate SVT → due to reflex PNS (vagal) outflow in Phase IV
- (3) Aid assessment of some heart murmur (I.e. murmurs of HOCM and MV prolapse $\uparrow$ in intensity with Valsalva, while all other murmurs $\downarrow$ with intensity)

(e) *To explain the cardiovascular changes accompanying the process of ageing.*

Heart:
- ↑ fibrous infiltration of myocardium → ↓ ventricular compliance (esp LV > RV) - ↓ # myocytes but compensated by hypertrophy → ↑ myocardial wall thickness (concentric) → ↓ ventricular compliance (esp LV > RV) - ↑ fibrous infiltration of endocardium → ↓ ventricular compliance (esp LV > RV) - Calcification of heart valves → valvular incompetence (stenosis/regurgitation)
Conducting system (I.e. SAN, AVN, bundle of His, Purkinje):
- ↑ fibrous/fatty infiltration - ↑ loss of pacemaker cells - ↓ # and sensitivity of β receptors within pacemaker cells
Peripheral vasculature:
- ↓ elasticity of large arteries due to thickening and calcification of vessel wall

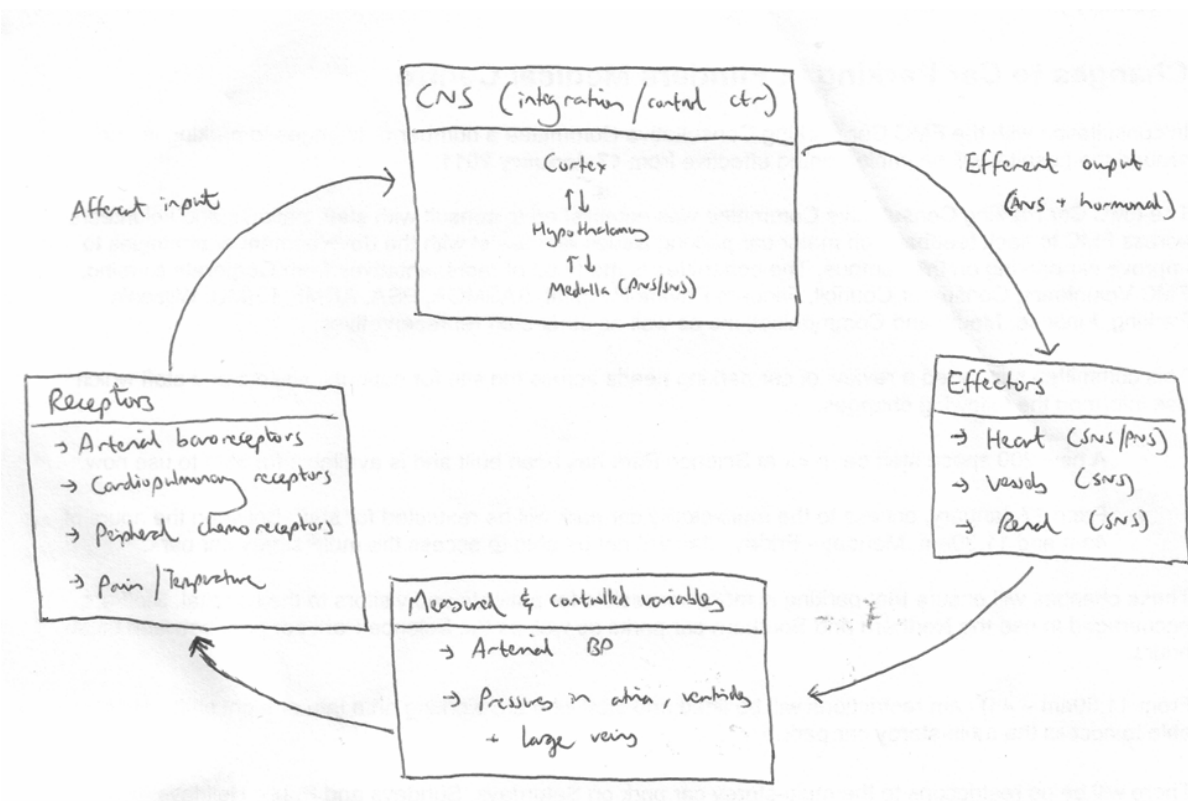
	Change with ageing	Reason
HR	- Resting HR → unchanged - ↓ maximum HR (Max. HR = 220 – age) - ↑ arrhythmias (AF, AV heart block, VEBs, BBB)	- Conduction system (SAN, AVN, bundle of His, Purkinje) → fibrous/fatty infiltration and loss of pacemaker cells - ↓ # and sensitivity of β receptor of pacemaker cells
SV	- ↓ resting SV - ↓ maximum SV	- ↓ ventricular compliance (2° to fibrous infiltration of myocardium/endocardium, and ventricular hypertrophy) - Valvular disease
C.O.	- ↓ due to preconditioning (I.e. sedentary lifestyle) or age-related disease - Unchanged in “healthy” subjects - Nb. ↑ C.O. occurs mainly by ↑ SV (preload) via Frank-Starling mechanism (rather than ↑ HR)	- ↓ HR – see above - ↓ preload (↓ SV) – see above - ↑ afterload (↑ SVR) – see below - ↑ reliance on “atrial kick” (30% of C.O. vs 5% in adults) → AF/↑HR not well tolerated
BP	- ↑ MAP and SBP - DBP ↑ slightly (until age 60), then ↓ - ↑ pulse pressure (due to ↑ SBP > DBP)	↓ elasticity of large arteries due to thickening and calcification of vessel wall
Pulmonary circulation	↑ PAP a/w ↑ PVR	
Control of CVS	- ↓ maximum exercise tolerance (due to age-related ↓ maximum HR, SV, C.O.) - Impaired BRR → postural hypotension - ↓ β receptor response of CVS to catecholamines (↓ # or affinity of receptor, ↓ post-receptor signalling, ↓ myocardial contractile response with stimulation) - ↑ vagal tone	



V. CONTROL OF CIRCULATION

- To describe the role of the vasomotor centre and autonomic nervous system in the regulation of cardiac output and venous return.*
- To describe the function of baroreceptors and to relate this knowledge to common clinical situations.*
- To explain the role of the autonomic nervous system in controlling systemic vascular resistance and redistribution of blood volume.*
- To explain the neural and humoral regulation of blood volume and flow.*

Control of the Cardiovascular System:



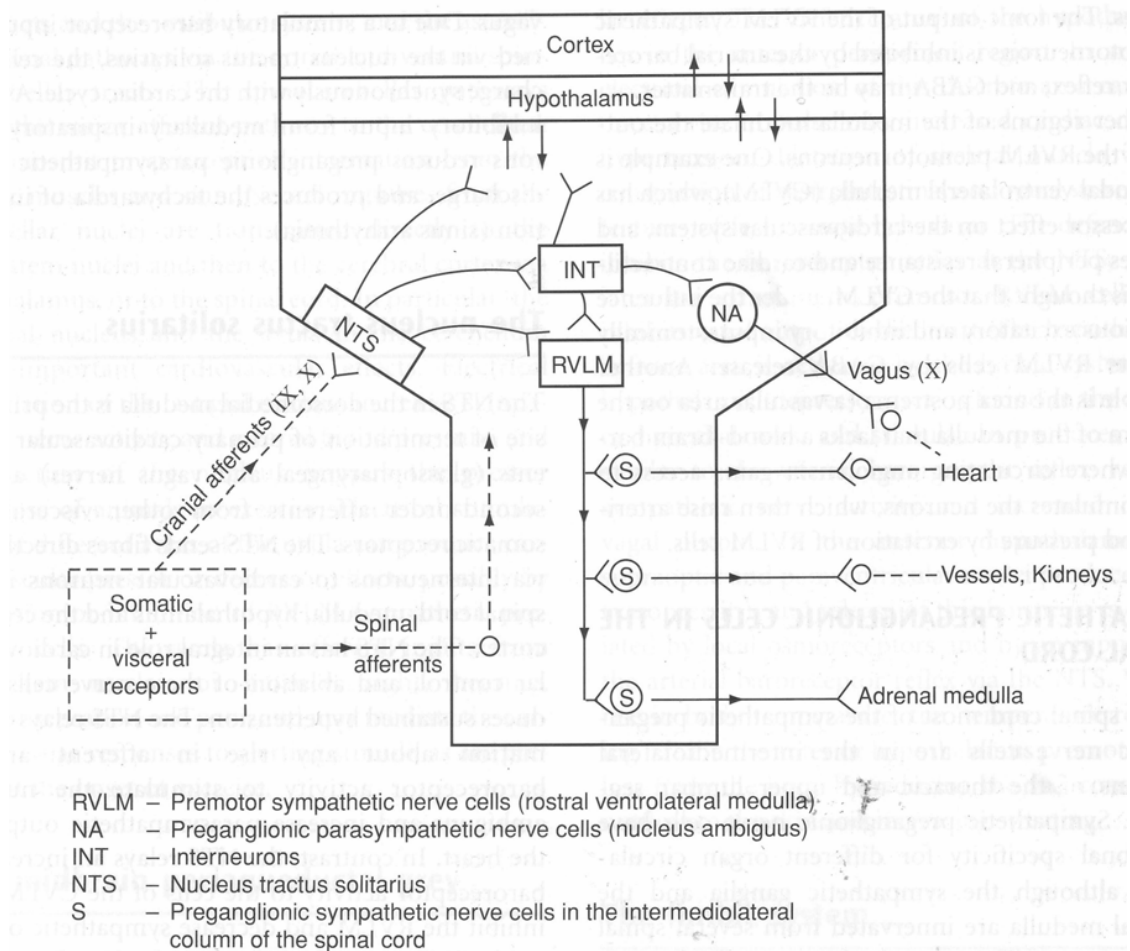
Central Nervous System Control of the CVS:

There are many centres in CNS that are involved in controlling the CVS:

- (1) Medulla (and spinal cord)
- (2) Cerebral cortex
- (3) Cerebellum
- (4) Hypothalamus
- (5) Periaqueductal grey
- (6) Limbic system

These centres control the CVS by:

- (i) Processing afferent information (Eg. from arterial baroreceptors, cardiopulmonary receptors, peripheral chemoreceptors, Etc.) in the medulla and higher brain centres
- (ii) Modulating SNS and PNS neuron activity within the medulla to produce an appropriate CVS response for the given situation (Eg. exercise, pain, haemorrhage, Etc.)



The main centres in the medulla and spinal cord include:

- (1) Central SNS nerve cells
 - o (a) Premotor sympathetic cells
 - 5 groups of cells within the medulla and pons influence preganglionic sympathetic nerve outflow:
 - (i) Rostral ventrolateral medulla (RVLM)
 - (ii) Rostral ventromedial medulla
 - (iii) Caudal raphe nuclei
 - (iv) Paraventricular nucleus of hypothalamus
 - (v) A5 NAd cell group in caudal ventrolateral pons
 - Rostral ventrolateral medulla (RVLM) is the MAIN group of cells → crucial to controlling arterial BP:
 - Has inherent (tonic) activity → basal SNS outflow to the heart and vessels produces resting CO and TPR (and BP)
 - Sends excitatory (glutamatergic) fibres that modulate preganglionic SNS nerves within the spinal cord
 - Receives input subserving CVS reflexes from other parts of the CNS (Eg. NTS, area postrema, CVLM, hypothalamus, higher brain centres) → mainly controlled by inhibitory arterial BRR (via GABA-mediated medullary interneurons)
 - o (b) Preganglionic sympathetic nerves
 - Located mainly in the intermediolateral column of the thoraco-lumbar region of the spinal cord (T1 to L2)

- Receives input – either excitatory inputs (via glutamate) or inhibitory inputs (via GABA) – from the medulla (esp tonic excitatory input from the RVLM) and spinal afferents (from skin, viscera and skeletal muscle)
 - These nerve fibres release ACh to innervate:
 - (i) Postganglionic sympathetic fibres within the sympathetic chain (or ganglia) → supplies the heart, vessels, and kidney
 - (ii) Adrenal medulla → causes direct release of catecholamines
- (2) Preganglionic parasympathetic nerve cells
 - Comprises of Nucleus ambiguus and Dorsal motor nucleus of the vagus within the ventrolateral medulla → send fibres via CN X to supply the atria of the heart
 - It is inherently quiescent (unlike the RVLM which is tonically active):
 - (i) Stimulated by the arterial BRR via the NTS → these cells discharge synchronously with the cardiac cycle during systole with the ↑ in BP, sending inhibitory vagal impulses to the atria
 - (ii) Directly inhibited by medullary inspiratory neurons → this produces sinus arrhythmia
- (3) Nucleus tractus solitarius
 - Located in the dorsomedial medulla:
 - Sends fibres directly and indirectly via medullary interneurons to other CVS neurons in CNS (esp to nucleus ambiguus and CVLM)
 - Receives inputs from primary afferents (CN X and IX), second-order afferents (other visceral and somatic receptors), and other CVS neurons within the CNS (Eg. cortex, hypothalamus, medulla)
 - Plays a role in:
 - (i) Relaying ↑ arterial BRR activity to the nucleus ambiguus (to ↑ PNS output to the heart) and CVLM (to ↓ RVLM activity and SNS output to the heart, vessels, kidney and adrenal medulla)
 - (ii) Modulating transmission of arterial BRR activity by altering its sensitivity (Eg. BRR activity is depressed by the “defence area” of the hypothalamus to allow appropriate rises in BP)
- (4) Medullary interneurons
 - Link afferent fibres with higher centres in the CNS (Eg. medulla, hypothalamus, cortex, Etc.), sympathetic premotor cells, and vagal preganglionic fibres
- (5) Afferent fibres:
 - Primary afferent fibres (via CN IX and CN X) from somatic and visceral receptors terminate at the NTS
 - Spinal afferent fibres from other visceral and somatic receptors also exist

The higher centres of the brain include:

- (1) Cerebellum → regulate CVS response to muscle/joint activity (Eg. exercise)
- (2) Midbrain periaqueductal grey → regulates CVS response to antinociception and threat reactions; also can provoke a “defence reaction” (similar to hypothalamus)
- (3) Hypothalamus
 - (i) “Defence area” → stimulates the RVLM (SNS output) and inhibits NA (PNS output) and the NTS (arterial BRR) → ↑ HR, ↑ C.O., skeletal muscle vasodilation, and renal/splanchnic vasoconstriction
 - (ii) “Depressor area” → produces similar effect as arterial BRR by attenuating SNS activity and enhancing vagal outflow
 - (iii) Supraoptic and paraventricular nuclei → stimulated by local osmoreceptors and input from arterial BRR (via NTS) to produce ADH (or vasopressin)
 - (iv) “Temperature regulation” area → causes heat loss from body by ↓ skin vasoconstriction and ↑ sweating
- (4) Limbic system → responsible for CVS changes a/w “fear/rage” and “defence” behaviours (Ie. ↑ HR, ↑ C.O., skeletal muscle vasodilation, and renal/splanchnic vasoconstriction); also produces “playing dead” reaction (associated with severe bradycardia and hypotension)

- (5) Cerebral cortex → vital for rapid CVS changes present with onset of exercise

Efferent Pathways and Effectors of the CVS:

- (1) ANS:
 - PNS nerve (via CN X) → activity limited to the heart, where there is ↓ SAN discharge and ↓ AVN conduction
 - SNS nerves (via T1 to L2) → causes +ve ino- and chronotropy (heart), arteriolar vasoconstriction and venoconstriction (vessels), and stimulation of renin release from the JGA of the kidneys (leading to RAA response)
- (2) Hormones:
 - Adr/NAd (from adrenal medulla) → causes +ve ino- and chronotropy (heart), and arteriolar vasoconstriction and venoconstriction (vessels)
 - ADH (from posterior pituitary) → causes ↑ H₂O reabsorption in the renal collecting ducts, and arteriolar vasoconstriction
 - RAAS → AII acts on the kidneys to conserve H₂O and electrolytes, stimulates SNS activity (central and peripheral), is a potent vasoconstrictor, and directly stimulates ADH secretion/thirst
 - ANF (from atrial cells) → causes natriuresis and ↑ H₂O excretion

Sensors and Measured Variables of the CVS:

Arterial BP is the primary measured variable in reflex control of the CVS:

- Arterial BP (or MAP) is determined by the amount of blood in the arterial system at any point in time. This is influenced by:
 - (i) C.O. → this determines the amount of blood entering into the aorta
 - (ii) TPR → this sets the blood flow into the capillaries, thereby dictating the amount of blood leaving the arteries into the peripheral capillaries

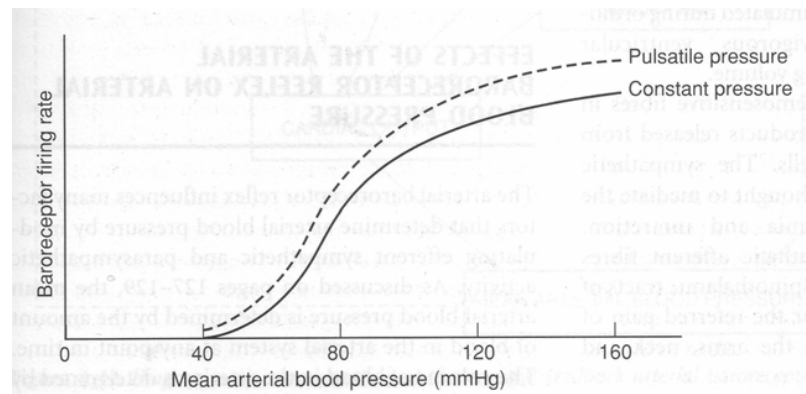
Thus, $MAP = CO \times TPR$

- Arterial BP is influenced by changes in either C.O. or TPR:
 - In the short-term → these factors are influenced mainly by the arterial BRR
 - In the long-term → these factors are influenced by body fluid balance (as controlled by RBF, RAAS, ADH, thirst/H₂O intake)

Sensors of the CVS:

- (1) Arterial baroreceptors:
 - Receptors are spray-like free nerve ending located within the walls of aortic arch (at transverse arch) and carotid sinus (at origin of ICA) → innervated mainly by unmyelinated C-fibres (few by large myelinated A-fibres) which send afferents via CN X and CN IX, respectively
 - These receptors are stimulated by ↑ arterial BP:
 - This causes the wall of aortic arch and carotid sinus to stretch → activates baroreceptors (Nb. pressure does NOT directly activate them!)
 - Impulses are sent to the NTS in the medulla via CN IX (from carotid sinus) and CN X (from aortic arch) → cause reflex inhibition of tonically-active SNS outflow (from the RVLM) and excitation of PNS outflow (via NA and the vagus nerve)
 - This leads to ↓ C.O. and TPR to attenuate the rise in arterial BP via – (i) -ve ino- and chronotropy of the heart, (ii) Venodilation, and (iii) Arteriolar vasodilation (↓ TPR)

- Within normal MAP, a proportion of arterial baroreceptors are active → during systole, there is a transient ↑ in baroreceptor activity due to the ↑ in arterial BP
- There is a relationship between arterial baroreceptor firing rate and arterial BP:
 - (i) Baroreceptor activity does not occur until MAP is > 60 mmHg, and activity is maximal when MAP is ~ 200 mmHg
 - (ii) Baroreceptor firing rate is proportional to MAP and pulse pressure
 - (iii) Small Δ in BP at “normal” BP (Eg. 100 mmHg) elicit greater changes in baroreceptor activity than at extremes of pressure
 - (iv) Each baroreceptor is active over a narrow pressure range → C-fibres have ↑ BP thresholds (more sensitive to ↑ pressures), while A fibres have ↓ BP threshold (more sensitive to ↓ pressures) → the combination of these fibres give a wide effective range of the BRR
 - (v) Baroreceptor firing rate at a given perfusion pressure is greater with “pulsatile” than with “constant” pressure



- Arterial BRR only provides short-term regulation of arterial BP (I.e. minimise transient fluctuations due to changes in posture):
 - This is because the baroreceptors can be reset to changes in BP → if the distending pressure is changed and held constant, the firing rate ↑ before returning to a “resting state”
 - This is caused by – (i) Opening of K^+ channels that cause the MP to return to the “resting” state at the new distending pressure, (ii) Resetting by central mechanisms (I.e. with exercise), or (iii) SNS activity to carotid sinus can ↑ firing rate at a given pressure
- (2) Cardiopulmonary receptors
 - (a) Veno-atrial stretch receptors
 - Low pressure stretch receptors located within endocardium in atria and pulmonary vessels → send afferents via myelinated vagal fibres
 - Two types – (i) Type A (fire during atrial contraction with “a” wave), (ii) Type B (fire during atrial filling with “v” wave)
 - Involved in limiting impact on BP of changes in blood volume by restoring it back to normal (“Bainbridge effect”) → stimulation causes (i) ↑ HR (due to SNS activity at SA node), (ii) ↑ natriuresis and H_2O excretion (due to inhibition of ADH secretion and renal SNS activity, and ↑ ANF production)
 - (b) Cardiac mechanoreceptors
 - Mechanoreceptors located mainly in LV → send afferents via unmyelinated vagal and sympathetic fibres
 - Involved in ↓ rises in arterial BP (“Bezold-Jarisch reflex”) → ventricular contraction causes these mechanoreceptors to fire, resulting in reflex bradycardia and hypotension (due to peripheral vasodilation)
- (3) Peripheral chemoreceptors (in the carotid and aortic bodies)

- Stimulated by hypoxia, hypercapnoea and acidosis → directly causes hypertension (through $\uparrow$ TPR) and bradycardia
- At low arterial BP where the BRR is not active (< 60 mmHg), the peripheral chemoreceptors (via severe hypoxia and acidosis) play a VITAL role in invoking a SNS outflow in response to severe hypotension
- (4) Other receptors:
 - Pain – Somatic pain causes tachycardia and hypertension, while visceral pain causes bradycardia and hypotension
 - Cold temperature causes hypertension
 - Bladder distension causes tachycardia and hypertension
 - “Diving response” (Ie. cold water stimulation of facial nerve) causes bradycardia and hypertension (via peripheral vasoconstriction)

(e) *To explain the integrated cardiovascular responses to exercise.*

Exercise is a/w extensive changes in CVS to meet the $\uparrow$ needs of O_2 /nutrient supply and removal of CO_2 , heat and metabolites from the body

The main CVS response to exercise is to $\uparrow$ blood flow to “working tissues” (Eg. skeletal muscle, heart, skin), while redistributing blood flow away from “non-working tissue” (Eg. GIT, kidneys):

- (1) $\uparrow$ skeletal muscle blood flow $\rightarrow$ to $\uparrow$ O_2 /nutrient delivery to meet the $\uparrow$ demands a/w energy (Eg. ATP) generation required for muscle contraction:
 - o Skeletal muscle receives 20% of C.O. (1 L/min) at rest $\rightarrow$ this $\uparrow$ to 80-90% of C.O. (20-30 L/min) with severe exercise
 - o This is due to:
 - (i) Local factors – $\uparrow$ muscle metabolism causes $\uparrow$ K^+ , ADP, H^+ , CO_2 , and temperature $\rightarrow$ causes local vasodilation
 - (ii) Systemic factors – $\uparrow$ C.O. and $\uparrow$ systemic BP

Note – During muscle contraction, intramuscular pressure $\uparrow$ $\rightarrow$ impedes muscle blood flow. This is important as there are two types of exercise:

- (a) Isotonic (dynamic) exercise – Usual form of exercise where muscle length changes $\rightarrow$ blood flow occurs during relaxation b/t muscle contraction
- (b) Isometric (static) exercise – Muscle length remains constant $\rightarrow$ continuous muscle contraction causes significant $\downarrow$ blood flow

Note – O_2 extraction can also be $\uparrow$ to satisfy $\uparrow$ O_2 demands $\rightarrow$ OHDC is shifted to the right due to $\uparrow$ CO_2 and H^+ (Bohr effect), $\uparrow$ temperature and $\uparrow$ 2,3-DPG

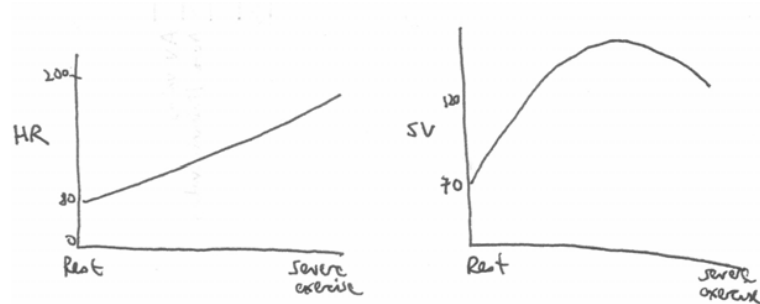
- (2) $\uparrow$ Coronary blood flow $\rightarrow$ to $\uparrow$ O_2 /nutrient delivery to meet $\uparrow$ demands of $\uparrow$ C.O.:
 - o CorBF is 250 mL/min at rest, but can $\uparrow$ to 1000 mL/min with severe exercise
 - o This is due to vasodilation 2° to local mechanisms or effects of circulating catecholamines on β_2 receptors in coronary vessels
- (3) $\uparrow$ skin blood flow $\rightarrow$ to dissipate heat
- (4) $\downarrow$ renal and splanchnic blood flow (due to $\uparrow$ SNS-induced vasoconstriction) $\rightarrow$ redistributes blood flow to skeletal muscle, heart and skin

Important to note – Cerebral blood flow is UNCHANGED (750 mL/min)

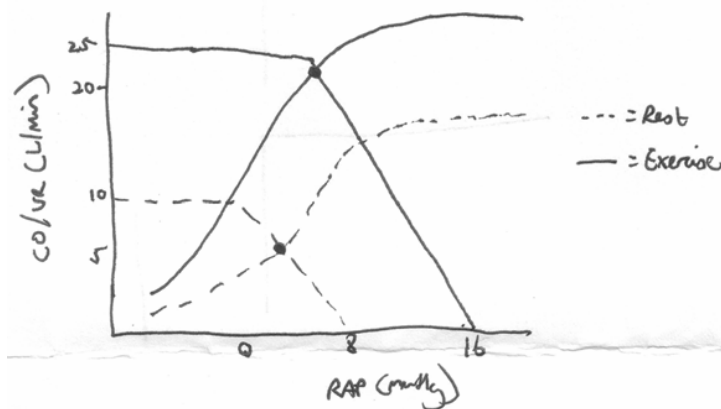
C.O. $\uparrow$ by 5X with exercise (from 5 L/min at rest, up to 20-30 L/min with severe exercise) $\rightarrow$ this is due to:

- (1) Muscle pump – Cyclic contraction of limb muscles cause intermittent compression of deep veins contract $\rightarrow$ facilitates venous return of blood to the heart (provided venous valves are competent)
- (2) Thoracic pump – During inspiration, intrathoracic pressure $\downarrow$ and intra-abdominal pressure $\uparrow$ $\rightarrow$ this compresses abdominal veins $\rightarrow$ facilitates VR back to heart (Nb. this is enhanced with $\uparrow$ depth and frequency of breathing)
- (3) SNS-mediated peripheral venoconstriction $\rightarrow$ $\downarrow$ venous capacitance, which $\uparrow$ VR back to heart
- (4) SNS-mediated peripheral vasoconstriction (esp splanchnic and renal circulation) $\rightarrow$ diverts blood flow to skeletal muscles, which then $\uparrow$ VR back to heart
- (5) Vasodilation of skeletal muscle vasculature due to local mechanisms (Ie. metabolites) $\rightarrow$ causes $\downarrow$ afterload 2° to $\downarrow$ SVR (EXCEPT during isometric (static) exercise, where afterload and SVR $\uparrow$ due to continuous compression of muscle vasculature)
- (6) $\uparrow$ HR and contractility

- $\uparrow$ C.O. is mainly due to $\uparrow$ HR $\rightarrow$ HR $\uparrow$ linearly (by 2-3x) with exercise up to a peak of 180-200 bpm $\rightarrow$ due to initial $\downarrow$ PNS (vagal) activity, followed by $\uparrow$ SNS activity
- SV can $\uparrow$ only 10-35% $\rightarrow$ SV $\uparrow$ non-linearly with exercise (mostly during light-moderate exercise; small $\uparrow$ with heavy exercise) $\rightarrow$ due to $\uparrow$ EDV (2° to $\uparrow$ VR to heart) and $\downarrow$ ESV (2° to $\uparrow$ emptying with $\uparrow$ SNS activity)



Effects on C.O. and VR curves:

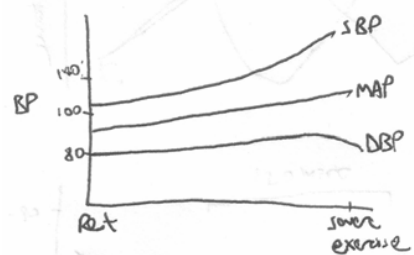


Note:

- $\uparrow$ C.O. due to $\uparrow$ HR/contractility
- $\uparrow$ MSFP due to $\uparrow$ VR from muscle pump, thoracic pump, and venoconstriction
- $\uparrow$ slope of VR curve due to $\downarrow$ resistance to venous return

Effects of exercise on BP is variable:

- (1) $\uparrow$ SBP and MAP (due to $\uparrow$ C.O.) $\rightarrow$ vital in providing driving pressure for blood flow to skeletal muscle, heart and skin
- (2) DBP unchanged, $\uparrow$ slightly, or $\downarrow$ (due to $\downarrow$ SVR a/w vasodilation in skeletal muscle)
- (3) Pulse pressure $\uparrow$ (by 2-3x)



Note – “Baroreceptor reflex” is set to a higher set-point with severe exercise to accommodate a $\uparrow$ in SBP and MAP

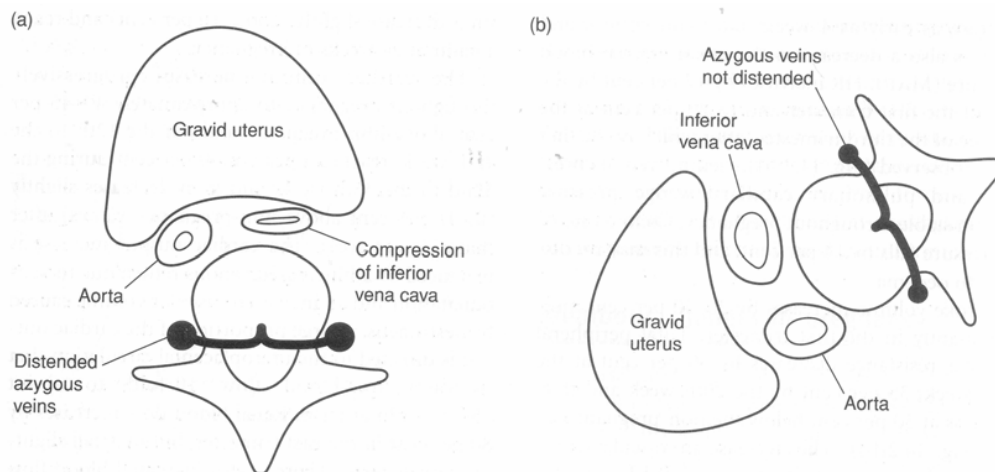
Of note, the CVS responses to exercise vary with the types of exercise:

- (a) Isometric (static) exercise $\rightarrow$ $\uparrow$ HR, $\uparrow$ BP (SBP, DBP and MAP) and $\uparrow$ C.O. $\rightarrow$ BUT b/c of continuous muscle contraction, the $\uparrow$ SVR and afterload causes (i) the $\uparrow$ in BP to be greater than the $\uparrow$ in C.O., and (ii) DBP to $\uparrow$ also
- (b) Isotonic (dynamic) exercise $\rightarrow$ $\uparrow$ HR, $\uparrow$ BP (SBP and MAP only) and $\uparrow$ C.O. $\rightarrow$ BUT b/c of intermittent muscle relaxation, the $\downarrow$ SVR and afterload causes (i) $\downarrow$ DBP (which causes a $\downarrow$ rise in MAP), (ii) $\uparrow$ rise in HR (in response to $\downarrow$ rise in MAP), (iii) $\uparrow$ rise in C.O.

(f) *To explain the integrated cardiovascular responses to pregnancy.*

CVS changes during pregnancy:

- (1) ↑ HR (by 15% at end of 1st TM → then by 25% by mid 3rd TM)
- (2) ↑ SV (by 20-30% from 8/40 to 32/40) → due to ↑ BV (40%)
- (3) ↑ C.O. (by 30% from 8/40 to 32/40) → due to ↑ HR, ↑ SV (a/w ↑ BV), ↓ TPR (a/w ↑ VR), and ↑ MRO₂
- (4) ↓ SVR (by 20-30% by end of 1st TM) → due to (i) placental circulation (10% of C.O.) acting as a low resistance AV shunt, and (ii) progesterone and PG-mediated peripheral vasodilation (esp renal, splanchnic, heart, breasts, skin circulation)
- (5) ↓ PVR (by 35% by end of 1st TM) → due to progesterone/prostaglandins
- (6) ↑ tissue blood flow (esp to uterus/placenta, heart, kidneys, GIT, breasts, skin) → due to (i) ↑ C.O. and (ii) hormone-mediated regional vasodilation – Nb. CBF is NOT affected!!!
- (7) ↓ BP (↓ MAP, ↓ DBP > ↓ SBP) by 10% (esp at 20/40) due to ↓ SVR → BUT this normalizes towards term
- (8) CVP and PCWP unchanged
- (9) Aortocaval compression
 - Abdominal aorta and IVC may be occluded by effects of gravid uterus as early as 2nd TM (max. effect at 36-38/40), especially when supine → characterised by:
 - (i) Complete compression of IVC:
 - 85% of ♀ – Compensatory vasoconstriction, tachycardia and collateral blood flow (venous return diverted via paravertebral and epidural veins into azygous system → SVC) maintains VR/C.O. and MAP
 - 15% of ♀ – “Supine hypotension syndrome” occurs as compensatory mechanisms are insufficient → results in ↓ VR/C.O. and MAP → causes hypotension, bradycardia, pallor, syncope, N/V, sweating
 - (ii) Partial compression of abdominal aorta → causes ↓ uteroplacental BF by 20% (causing foetal distress) and ↓ renal BF
 - This is prevented by positioning mother on left side



Note – During labour:

- (i) C.O. – ↑ 15% (early labour), ↑ 30% (1st stage), ↑ 45% (2nd stage), ↑ 65% (post-partum), then normalizes 2/52 post-partum
- (ii) Uterine contractions and uterine involution post-partum squeezes 300 mL of blood out of uterus into circulation (“Autotransfusion”) causes ↑ VR → ↑ SV/C.O.
- (iii) BP – ↑ 10-20 mmHg with uterine contractions. Normalises 2/52 post-partum
- (iv) CVP ↑ (4-6 cmH₂O) due to ↑ VR a/w autotransfusion

(g) ***To explain the integrated cardiovascular responses to anaesthesia and central neural blockade.***

(I) Cardiovascular responses to anaesthesia:

CVS responses to volatile agents:

- (i) HR – Some blunt BRR/SNS response (sevoflurane, halothane) and cause ↓ HR or no changes in HR. Some retain BRR/SNS response (desflurane, isoflurane) and cause reflex ↑ HR 2° to ↓ C.O./BP. Halothane is a/w junctional rhythm/bradycardia due to ↑ vagal tone and direct SAN/AVN depression
- (ii) C.O. – All volatiles depress myocardium and ↓ myocardial contraction (esp halothane), but intact BRR/SNS response (desflurane, isoflurane, N₂O) can maintain C.O. due to reflex ↑ HR. Those with blunted BRR/SNS response (sevoflurane, halothane) have ↓ C.O.
- (iii) BP – All volatiles have ↓ BP (most with halothane) due to ↓ SVR and/or ↓ C.O., except N₂O which has unchanged BP due to intact SNS response
- (iv) SVR – All agents ↓ SVR (except for halothane, which is unchanged)
- (v) PVR – All agents ↓ PVR due to impaired HPV (except N₂O, which ↑ PVR)
- (vi) Arrhythmogenic potential – All agents prolong QTc (risk of Torsades de Pointes), but halothane sensitises myocardium to arrhythmogenic effects of catecholamines (risk of VEB, VT, VF)
- (vii) Most agents (esp isoflurane, desflurane, sevoflurane) possess “ischaemic preconditioning”
- (viii) All agents ↓ myocardial O₂ demands but effects on coronary BF is variable

CVS responses to induction agents:

- (i) HR – STP causes ↑ HR (due to intact BRR/SNS output); Ketamine cause ↑ HR (due to direct central SNS outflow and inhibition of NAd reuptake centrally and peripherally); Propofol causes ↓ HR (due to blunted BRR/SNS output and ↑ vagal outflow); Etomidate has minimal change in HR (due to intact BRR/SNS output)
- (ii) C.O. – All agents are direct myocardial depressants, but change in C.O. is minimal for STP (and even less so for Etomidate) due to intact BRR/SNS output; Propofol causes ↓ C.O. (as BRR/SNS output is blunted); Ketamine causes ↑ C.O. due to indirect SNS effects
- (iii) BP – All agents cause ↓ BP, although it is mild with STP and Etomidate; Propofol causes significant ↓ BP; Ketamine causes ↑ BP
- (iv) SVR – All agents cause ↓ SVR due to peripheral vasodilation; SVR is unchanged with ketamine
- (v) Myocardial O₂ balance – STP and ketamine ↑ MRO₂ and CBF; Propofol has the opposite effect; Etomidate MRO₂/CBF is stable

CVS responses to opioids:

- (i) HR – All opioids cause ↓ HR → due to ↑ CN X (vagal) nuclei output, blunting of BRR and direct depression of SAN/AVN (EXCEPT pethidine which ↑ HR due to anticholinergic effect)
- (ii) C.O. – All opioids can ↓ C.O. due to ↓ HR and blunted BRR (however, they have no direct myocardial depressive effects)
- (iii) BP – All opioids can ↓ BP due to ↓ C.O. and blunted BRR (but especially morphine and pethidine due to peripheral vasodilation 2° to histamine release)

CVS responses to local anaesthetics:

- LAs depress conduction of cardiac impulse → can be therapeutic (Eg. treat ventricular arrhythmias)
- BUT at toxic levels (Ie. accidental IVI) can cause transient CVS excitation initially (Eg. ↑ HR and BP), but later CVS depression (Eg. bradycardia, AVHB, profound hypotension, cardiac arrest)

CVS responses to controlled ventilation:

- Effect of IPPV and PEEP:
 - o Cause ↓ C.O. 2° to ↑ intra-thoracic pressure, which ↓ VR and preload (See “Applied aspects of CVS physiology”)
- Changes in PaCO₂ due to changes in ventilation
 - o ↓ PaCO₂ (esp during controlled ventilation) → causes ↓ C.O. (due to ↑ peripheral vasoconstriction, which ↑ SVR and afterload), and ↓ CBF and ICP (due to ↑ cerebral vasoconstriction)
 - o ↑ PaCO₂ (esp during spontaneous ventilation) → causes ↑ peripheral vasodilation and ↑ SNS activity → leads to ↑ C.O. but also ↑ risk of arrhythmias (esp with halothane)

(II) Cardiovascular responses to central neural blockade:

Central neural blockade → involves injection of LA into CSF (spinal anaesthesia) or epidural space (epidural or caudal anaesthesia), which then acts on nerve roots in the subarachnoid or epidural space, respectively, to produce regional anaesthesia

CVS effects of central neural blockade are caused by interruption of efferent ANS transmission → involves mainly ↓ SNS tone (“sympathectomy”), which can be accompanied by unopposed PNS tone

Remember:

- SNS outflow → from small, myelinated preganglionic nerves exiting lateral horn of spinal cord b/t T1-L2
- PNS outflow → from cranial and sacral nerves

So central neural blockade can completely block SNS outflow from T1-L2, but NOT PNS outflow as CN X (vagus) is not affected (only PNS outflow from sacral nerves can be blocked)

The CVS effects of central neural blockade are proportional to the degree (or level) of sympathectomy (and unopposed vagal tone):

(1) Sacral blockade only:

- Blockade of sacral PNS outflow only → minimal effects on peripheral vascular tone → thus, minimal CVS effects

(2) Lumbar blockade:

- ↓ C.O. and ↓ BP occurs due to sympathectomy of SNS fibres that arise from T5-L1 → causes ↓ SNS-mediated vasomotor tone of arteries and veins as follows:
 - o (i) Venodilation of venous (capacitance) vessels → results in ↑ pooling of blood and ↓ venous return to the heart
 - o (ii) Vasodilation of arterial (resistance) vessels → results in ↓ SVR

Important to note – Venodilation of capacitance vessels have a **GREATER** effect on ↓ BP and C.O. (cf. vasodilation of resistance vessels) b/c:

- (i) 75% of blood volume exists in the venous circulation
- (ii) Denervated arterioles retain their intrinsic tone → do NOT maximally dilate
- (iii) Reflex arteriolar vasoconstriction occurs in vascular beds with intact SNS response (I.e. above level of block) → minimise ↓ in SVR

- Compensatory reflexes are activated to offset the ↓ C.O. and BP:
 - o (i) High pressure “baroreceptor reflex” (BRR) → carotid sinus and aortic arch

- Respond to ↓ stretch due to ↓ BP → stimulates brainstem vasomotor centres to ↓ inhibitory input to SNS → causes:
 - ↑ HR and myocardial contractility → to ↑ C.O.
 - Compensatory vasoconstriction above level of blockade → ↑ SVR
 - Venos constriction above level of blockade → mobilise blood from lung, skeletal muscle, skin, liver, Etc. to ↑ VR
 - Activate RAAS (via direct β_1 stimulation) and ↑ ADH from pituitary → cause vasoconstriction and ↑ $\text{Na}^+/\text{H}_2\text{O}$ retention
- (ii) Low pressure BRR → RA and great vessels
 - Respond to ↓ stretch due to ↓ BP → causes ↓ ANP secretion → ↓ $\text{Na}^+/\text{H}_2\text{O}$ loss and ↓ inhibition of RAAS/ADH system

(3) Mid-thoracic blockade:

- Renal compensatory mechanism are invoked to preserve renal blood flow – ↓ RBF 2° to ↓ BP/↓ C.O. results in ↓ stretching of afferent renal arterioles at JG apparatus, which activates RAAS → ↑ AII → results in ↑ RBF (and ↓ GFR)

(4) High-thoracic blockade:

- Profound ↓ BP and ↓ C.O. occur due to sympathectomy of SNS “cardiac accelerator” fibres that arise from T1-T4 → causes:
 - (i) ↓ HR and ↓ myocardial contractility
 - (ii) Loss of compensatory arteriolar vasoconstriction → ↓ SVR
 - (iii) Further venodilation of capacitance vessels → ↓ venous return
 - (iv) Loss of intact baroreceptor response to counter ↓ BP

Note – Profound bradycardia and cardiac arrest can occur due to unopposed PNS (vagal) tone

(5) Brainstem:

- Profound high blocks affecting the brainstem inhibit the vasomotor centre in medulla → central inhibition of SNS outflow → profound and life-threatening ↓ BP and ↓ C.O. → cardiac arrest

CVS effects of central neural blockade are exaggerated by certain factors:

- (i) Hypovolaemia → further ↓ VR, causing profound ↓ BP and C.O.
- (ii) Elderly → impaired physiological reserve to compensate for ↓ BP and C.O.
- (iii) Head-up positioning → further ↓ VR, causing profound ↓ BP and C.O.
- (iv) Weight of gravid uterus → further ↓ VR, causing profound ↓ BP and C.O.
- (v) Fixed C.O. state (Eg. AS) → unable to compensate for ↓ BP and C.O.

Note – To minimise these CVS effects:

- (i) Volume load with IVF to compensate for venous pooling and ↓ VR
- (ii) Auto-transfuse with head-down positioning to ↑ VR
- (iii) Left uterine displacement in 3rd TM pregnancy to remove physical obstruction to VR
- (iv) Consider pharmacological management – Atropine for ↓ HR and vasopressors (Eg. ephedrine, metaraminol) for ↓ BP

Important to note – “Bezold-Jarisch reflex”

- Mechanoreceptors in LV that are activated during ventricular contraction → cause reflex vasodilation and bradycardia
- During central neural blockade (esp with severe hypovolaemia or upright posture), where compensatory tachycardia and vasoconstriction are vital to preserve BP, vigorous contraction of underfilled ventricle (2° to ↓ venous return) triggers this reflex causing marked ↓ BP and C.O. (and even cardiac arrest)

III. DETERMINANTS AND CONTROL OF CARDIAC OUTPUT

(a) **To explain the Frank-Starling mechanism and its relationship to excitation-contraction coupling.**

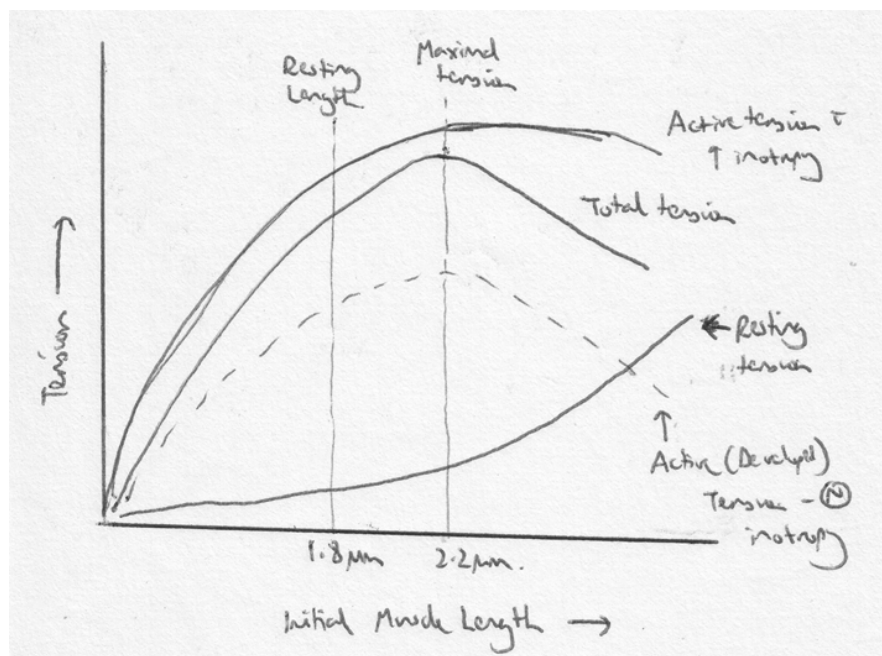
Definition the Frank-Starling mechanism:

- This mechanism describes an intrinsic phenomenon where the initial resting length of the ventricular fibres at end-diastole (which is influenced by the ventricular preload) determines the force of contraction of the ventricular muscle
- This allows the heart to be able to change its cardiac output (via changes in stroke volume) in response to variations in its venous return

For example. A rise in venous return $\rightarrow$ increased ventricular filling $\rightarrow$ increased cardiac myocyte stretching prior to contraction $\rightarrow$ Increased ventricular preload (a/w a rise in ventricular EDV and EDP) $\rightarrow$ Increased stroke volume to compensate for the rise in venous return

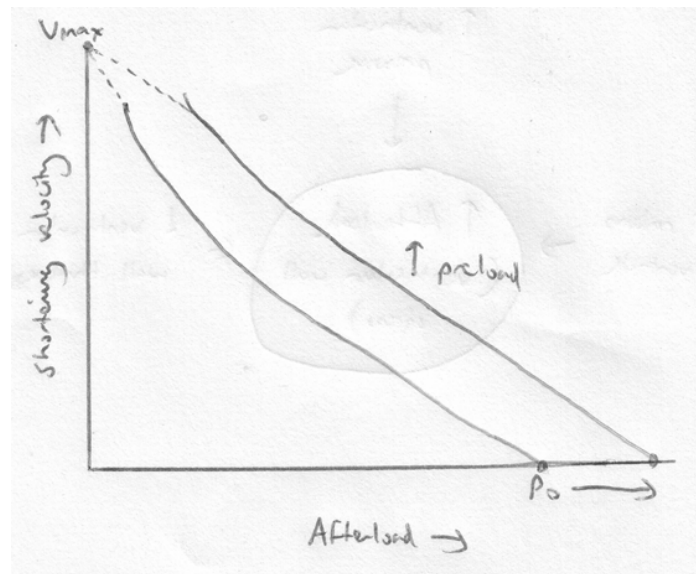
Basis of the Frank-Starling mechanism:

- Length-tension relationship for cardiac muscle:
 - o Active tension developed during isometric contraction (I.e. muscle length is fixed against a load) is PROPORTIONAL to the initial resting length of the cardiac muscle (or preload)
 - o However, this relationship occurs up to a sarcomere length of $2.2\ \mu\text{m}$ where maximal active tension is achieved – With further sarcomere stretching, tension then decreases (Nb. sarcomeres cannot be stretched much $> 2.2\ \mu\text{m}$ due to increased stiffness of cardiac muscle, hence the descending part of the curve is not seen)
 - o Multiple length-tension relationships exist because active tension at a given initial resting length of cardiac muscle is dependent on its inotropic state – With increased inotropy, the curve shifts to the left (I.e. more tension at a given length); opposite occurs with decreased inotropy



- Force-velocity relationships for cardiac muscle:
 - o At a given afterload and inotropic state, a larger initial resting length of cardiac muscle (or preload) causes an:
 - (i) Increase in velocity of cardiac fibre shortening

- (ii) Increase in maximal isometric force (P_0) – Nb. this occurs when the afterload is so great that the muscle fibre cannot shorten, thus the afterload here equals the maximal isometric force the muscle can generate



Cellular mechanism of the Frank-Starling mechanism:

Initial resting length of cardiac myocytes influences twitch tension and the force of contraction by:

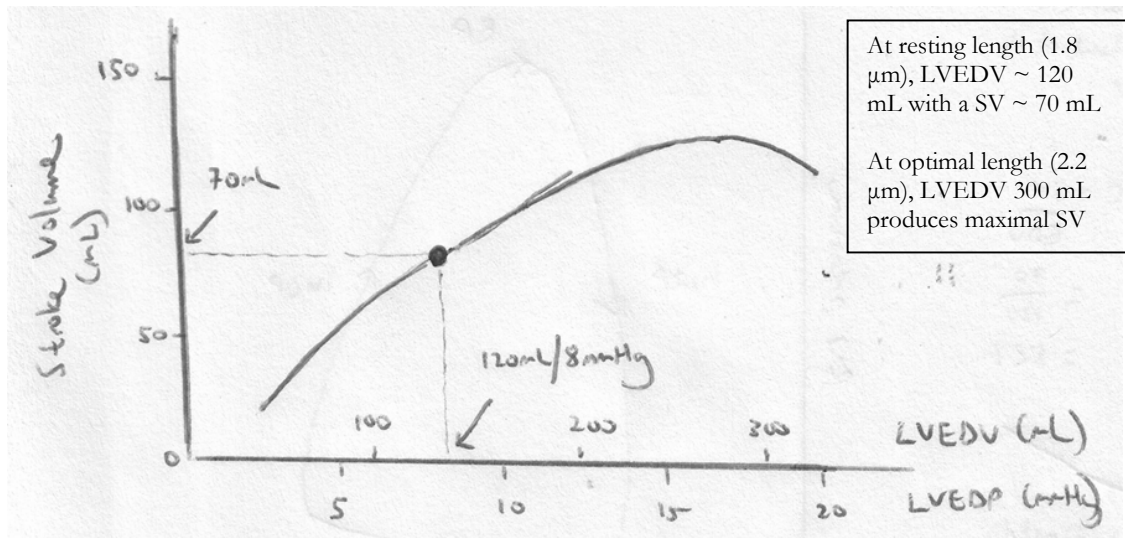
- (1) The degree of overlap of contractile actin-myosin fibres (I.e. number of actin-myosin cross-bridges formed) as per the “Sliding Filament Theory”:
 - At normal resting length ($1.8 \mu\text{m}$), this overlap (and the number of cross-bridges formed) is suboptimal, thus leading to a suboptimal twitch tension
 - With increasing resting length (up to $2.2 \mu\text{m}$), there is better overlap (and cross-bridging) of the actin-myosin fibres, thereby leading to greater twitch tension
 - Overstretching ($> 2.2 \mu\text{m}$) results in suboptimal actin-myosin overlapping (and cross-bridging) again, which leads to a fall in twitch tension
- (2) The sensitivity of troponin C to Ca^{2+} and the intracellular [] of free Ca^{2+} :
 - With increasing resting length, there is increased sensitivity of troponin C to Ca^{2+} and increased intracellular [] of free Ca^{2+}

Excitation-contraction coupling is the process by which an electrical stimulus on the myocyte is converted to a mechanical response:

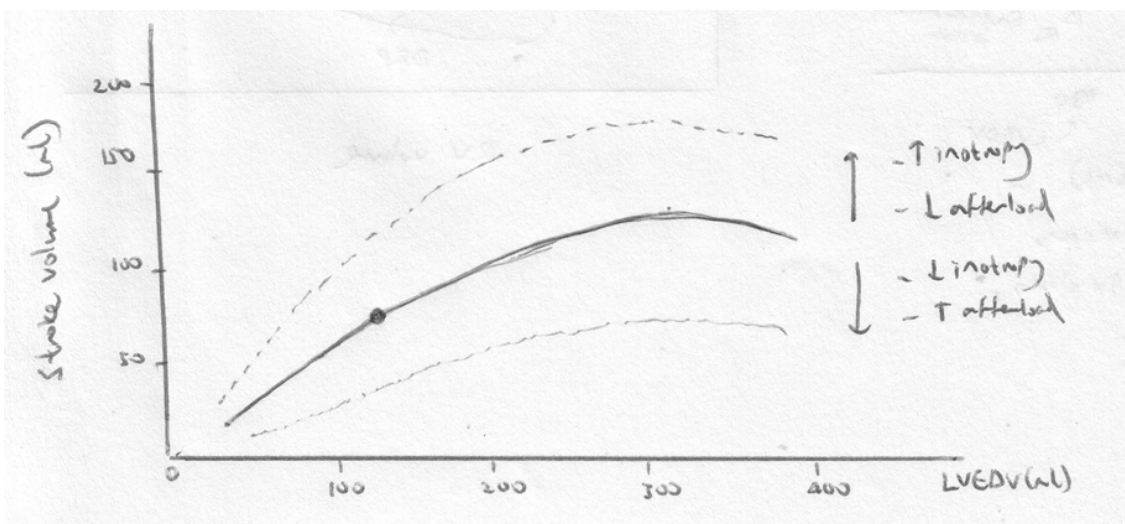
- AP arriving at the cell membrane causes influx of Ca^{2+} from outside the myocyte, which then stimulates release of Ca^{2+} from the SR, thus significantly increasing IC $[\text{Ca}^{2+}]$
- Increased binding of Ca^{2+} to Troponin C leads to a conformational change in the trimeric troponin complex that causes Troponin I to move tropomyosin. This uncovers the actin binding site allowing the myosin head to bind and form a cross bridge
- ATP hydrolysis by myosin ATPase powers “cross bridge cycling” (I.e. conformational change in actin-myosin complex), which shortens the sarcomere length and provides increased twitch tension
- This continues until IC Ca^{2+} decreases or ATP supply is diminished

Frank-Starling Curve:

- This curve demonstrates the relationship between ventricular preload (as assessed by LVEDV or LVEDP) and change in stroke volume – Normally, the heart will lie on the ascending part of the curve, such that an increase in LVEDV or LVEDP will lead to a rise in SV



- A family of curves exist depending on the afterload or contractility state of the heart:
 - (i) Afterload – Increased afterload decreases the velocity of fibre shortening as demonstrated by the force-velocity relationship. Since the duration for systolic ejection is finite (~ 200 msec), this reduces the rate of volume ejection such that more blood remains within the ventricle at end-systole (I.e. increased ESV and reduced SV). This causes the curve to shift down and to the right (I.e. decreased SV at a given LVEDP or LVEDV)
 - (ii) Contractility – Increased inotropy increases the total (or active) tension at a given preload as demonstrated by the length-tension relationship. This causes the curve to shift up and to the left (I.e. increased SV at a given LVEDP or LVEDV)



(b) *To define preload, afterload and myocardial contractility.*

(c) *To describe the factors that determine preload, afterload and myocardial contractility.*

Preload:

Definition of preload:

- The load on the myocardium that determines the initial stretching (or fibre length) of the cardiac myocytes prior to onset of contraction (i.e. end-diastole)

Indices of preload:

- Since myocyte fibre length cannot be directly measured, the load causing the initial stretching of the cardiac myocyte prior to contraction (or preload) must be indirectly determined using either:
 - (a) Ventricular end-diastolic volume (EDV)
 - LVEDV and RVEDV can be easily measured by TTE and used to indirectly assess LV and RV preload, respectively
 - (b) Ventricular end-diastolic pressure (EDP)
 - Ventricular EDP and EDV are related by the ventricular wall compliance

$$\text{Ventricular compliance} = \frac{\text{Ventricular EDV}}{\text{Ventricular EDP}}$$

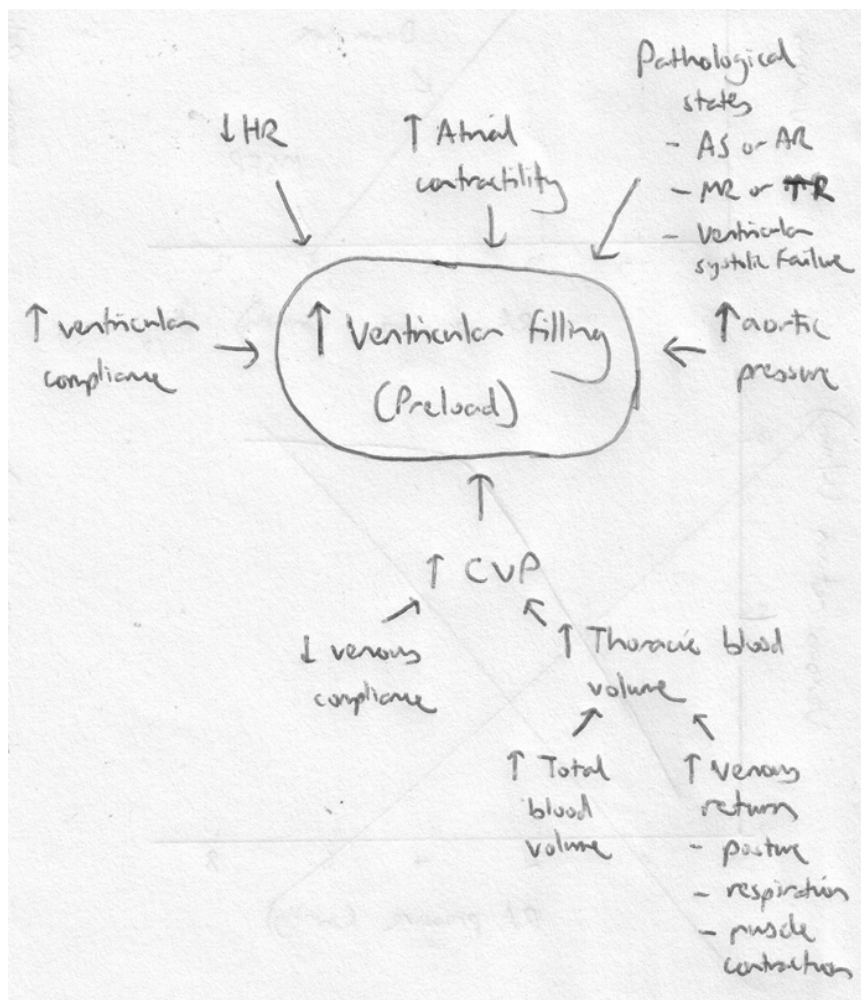
- EDP is not an ideal measure of preload due to situations where there is altered ventricular compliance (Eg. ventricular distension)
- LV EDP as a measure of LV preload can be measured using:
 - (i) LA pressure (via a left heart catheter study) – During diastole, a low resistance path between the LA and LV exists due to an open MV, thus LAP $\approx$ LVEDP (EXCEPT in the presence of mitral valve disease)
 - (ii) Pulmonary capillary wedge pressure (via Swan-Ganz catheter study) – Occlusion of the PA by a balloon-tipped catheter stops blood flow in the vessel, thereby disrupting the pressure drop along it. The pressure measured at the catheter tip should then be equal as that downstream where flow resumes due to joining from other vessels. This pressure should approximate LAP ($\approx$ LVEDP) as the path from the pulmonary vessels to the LA is low resistance and at the same horizontal level
 - (iii) RA pressure or CVP (via a CVC line) – RV preload is assumed to be similar to LV preload
- RV EDP as a measure of RV preload can be measured using RAP and CVP (via a CVC line)

Factors that determine preload:

- (1) Central venous pressure
 - (a) Venous compliance – Increased venomotor tone (Eg. venoconstriction) leads to a rise in CVP, which increases ventricular preload. Opposite outcome occurs with reduced venomotor tone (Eg. venodilation)
 - (b) Thoracic venous blood volume
 - (i) Total blood volume – Increased total blood volume states (Eg. hypervolaemia) leads to a rise in CVP, which increases ventricular preload. Opposite outcome occurs with decreased total blood volume states (Eg. hypovolaemia)
 - (ii) Venous return – Increased venous return (such as due to increased respiration, skeletal muscle contraction or head-tilt down posturing) leads

to a rise in CVP and ventricular preload. Opposite outcome occurs with decreased venous return

- (2) Ventricular compliance – Increased compliance leads to enhanced ventricular expansion during filling at a given filling pressure, thus increasing its preload. Opposite outcome occurs with decreased ventricular compliance
- (3) Atrial contractility – Increased atrial contractile force (Eg. due to SNS stimulation or increased atrial filling) leads to increased ventricular preload. Opposite outcome occurs with decreased atrial contractile force (Eg. with AF)
- (4) HR – Increased HR impairs ventricular filling time, which decreases ventricular preload. Opposite outcome occurs with decreased HR
- (5) Aortic pressure – Increased afterload (or raised aortic pressure) reduces SV by increasing ESV, which leads to a secondary rise in EDV (or ventricular preload). Opposite outcome occurs with decreased afterload
- (6) Pathological conditions
 - o Increased preload occurs with – Ventricular systolic failure, outflow valve stenosis or regurgitation (AS or AR), inflow valve regurgitation (MR/TR)
 - o Decreased preload occurs with – Ventricular diastolic failure, inflow valve stenosis (MS/TS)



Afterload:

Definition of afterload:

- Ventricular wall stress encountered as a result of the resistance that the ventricle must overcome for it to eject its contents into the arterial circulation during systole (I.e. following isovolumetric ventricular contraction and opening of the aorto-pulmonary valves)

Indices of afterload:

- The Law of LaPlace can be used to determine “ventricular wall stress”:

$$\text{Ventricular wall tension (T)} = \frac{\text{Ventricular pressure (P)} \times \text{Radius of the ventricle (r)}}{2}$$

$$\text{And, } T = \frac{\text{Ventricular wall stress } (\sigma)}{\text{Ventricular wall thickness (h)}}$$

$$\text{Thus, } \sigma = \frac{(P \times r)}{2h}$$

- Ventricular wall stress is therefore indirectly measured by the ventricular pressure during systolic ejection ($\approx$ aortic pressure, UNLESS AS is present) – Clinically this is estimated by the systolic arterial BP (or more commonly the MAP)

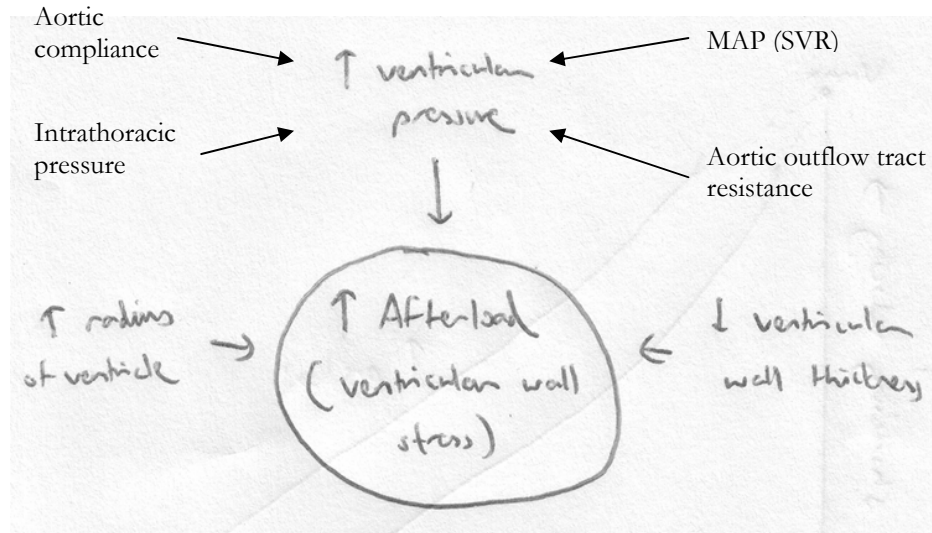
Factors that determine afterload:

- (1) Ventricular pressure
 - o Increased ventricular pressure causes a rise in afterload
 - o This pressure is influenced by:
 - (a) Systemic arterial pressure (or MAP), which is determined by systemic vascular resistance (SVR) – MAIN factor of afterload (increased MAP and SVR lead to increased afterload)
 - SVR is the sum of resistances to blood flow through all parallel vascular beds of the systemic circulation
 - $\text{SVR} \sim 18 \text{ mmHg/L/min}$ or $900\text{-}1200 \text{ dynes}\cdot\text{sec}/\text{cm}^5$
 - It is determined by Poiseuille’s Law:

$$R = \frac{8\eta L}{\pi r^4}$$

- o (i) Increased blood viscosity (Eg. polycythaemia) will increase SVR and afterload
- o (ii) Decreased vessel length (Eg. shunting) will decrease SVR and afterload
- o (iii) Arteriolar radius is the MAIN factor determining SVR and afterload:
 - SNS stimulation (NAd/Adr) causes vasoconstriction and increased SVR/afterload
 - Myogenic autoregulation – Reflex vasoconstriction in response to increased vessel wall stretch to limit pressure (and blood flow) to tissues
 - Local metabolic autoregulation – Vasodilation in response to increased tissue metabolism (low PO_2 , high PCO_2 , K^+ , low pH, lactic acid, Etc.)
- (b) Aortic outflow tract resistance (Eg. valvular resistance such as AS; HOCM) – Increased resistance leads to increased afterload
- (c) Aortic compliance – Compliances decreases with age, leading to increased afterload
- (d) Intrathoracic pressure – Positive intrathoracic pressure (Eg. IPPV, tension PTX, haemothorax) squeezes the heart, which increases the pressure gradient between the LV and extra-thoracic tree. This aids ejection of blood and decreases afterload

- (2) Ventricular radius
 - Increased radius (Eg. LV dilation, overfilling, cardiomyopathy) leads to increased afterload
- (3) Ventricular wall thickness
 - Increased thickness (Eg. ventricular hypertrophy) leads to reduced afterload



Contractility:

Definition of contractility:

- Intrinsic ability of the myocardial fibre to shorten and thus increase the force of contraction that is independent of preload, afterload and heart rate
- It is a feature unique to cardiac muscle (Ie. not seen in skeletal muscle)

Indices of contractility:

- $(dp/dt)_{\max}$ is the maximum rate of change of pressure in LV during isovolumetric contraction that can be measured using a LV catheter study
- It correlates with contractility (in that there is a greater rate of rise in maximal pressure with more forceful contractions) – BUT this index is NOT independent of preload and afterload

Mechanism of inotropy:

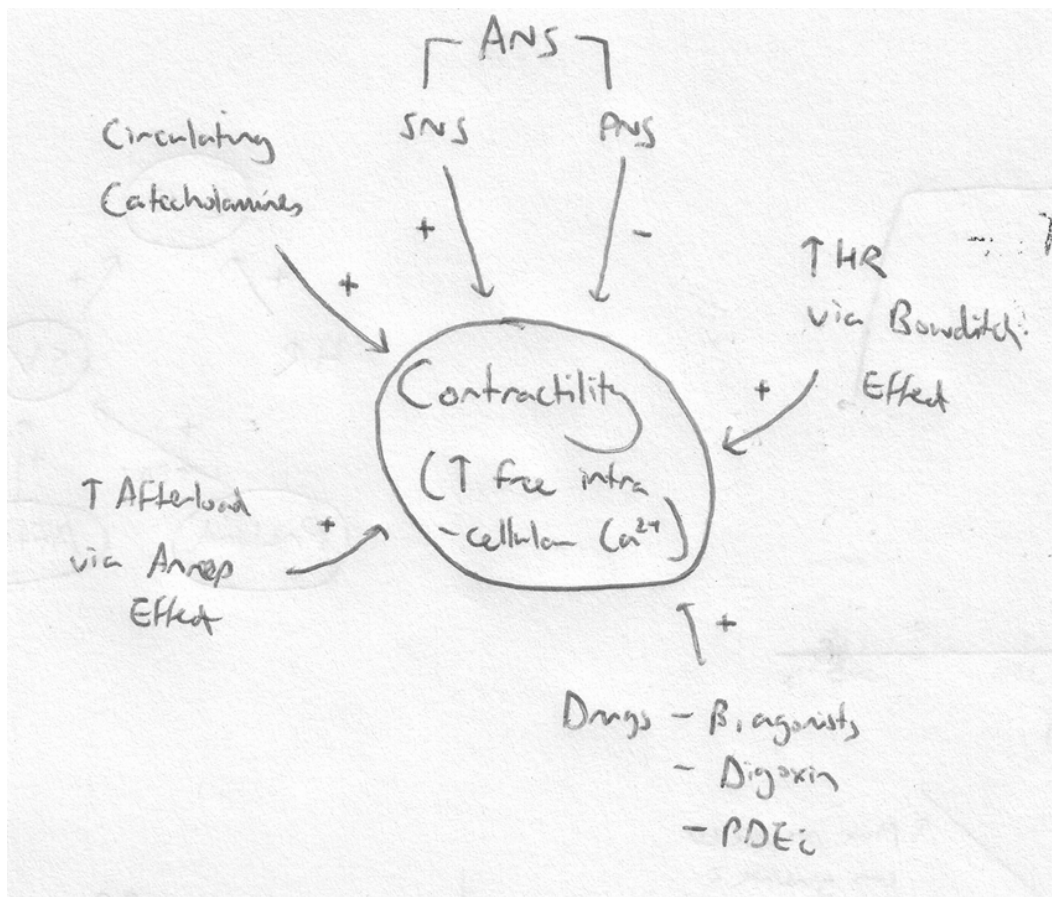
- Most signal transduction pathways that stimulate inotropy involve free IC Ca^{2+} by:
 - (1) Increasing its influx (via L-type Ca^{2+} channels) during the cardiac AP (primarily during phase 2)
 - (2) Increasing release of Ca^{2+} by the SR
 - (3) Sensitizing troponin C to Ca^{2+}

Factors that determine contractility:

- (1) ANS (main factor)
 - SNS nerves – Prominent role in regulating ventricular and atrial inotropy

Nb. Beta-adrenoceptor stimulation leads to – (i) Increased IC cAMP which enhances Ca^{2+} entry via L-type Ca^{2+} channels (increases contraction) and Ca^{2+} sequestration into the SR via phosphorylation of phospholamban via a cAMP-dependent protein kinase (increases relaxation); (ii) Increased IC IP₃ which triggers Ca^{2+} release from the SR

- PNS nerves (Vagal) – Significant –ve inotropic effect in atrial only (little impact on ventricle)
- (2) Circulating catecholamines – Augments SNS adrenergic effect
- (3) Afterload
 - Via the “Anrep Effect”, an abrupt increase in afterload can cause a small rise in inotropy through an unknown mechanism
 - This rise in inotropy partly compensates for the increase in ESV and fall in SV associated with increased afterload (I.e. if this effect was absent, the fall in SV would be more substantial than what is actually observed)
- (4) Heart rate
 - Via the “Bowditch effect”, an increase in HR stimulates inotropy via the “Treppe effect”
 - This is due to the inability of the Na^+/K^+ ATPase to keep up with the Na^+ influx at higher HR, which leads inhibition of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and eventual accumulation of free IC Ca^{2+}
- (5) Drugs
 - Digoxin – Inhibits Na^+/K^+ ATPase, which leads to a rise in IC Na^+ that inhibits the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and cause an accumulation of IC Ca^{2+}
 - Beta-adrenoceptor agonists (Eg. DA, Dobutamine, Adr, INE) (See beta-adrenoceptor stimulation for mechanism)
 - PDEi (Eg. milrinone) – Inhibits breakdown of IC cAMP (See beta-adrenoceptor for mechanism)



- (d) *To describe myocardial oxygen demand and supply, and the conditions that may alter each.*

Myocardial O₂ supply:

- Myocardial O₂ supply is 16 mL O₂/min/100 g (or 45-50 mL O₂/min for a 300 g heart) at rest – This can increase by 3-4X mainly by increases in CBF (but not CaO₂) in response to increasing myocardial O₂ demand or consumption!

$$\text{Myocardial DO}_2 = \text{CBF} \times \text{CaO}_2$$

- Myocardial O₂ supply is determined by the following factors:
 - (1) Arterial content of O₂ (CaO₂):
 - CaO₂ is 20 mL O₂/100 mL blood. It is determined by:
 - (a) O₂ bound to Hb (main factor) – Influenced by [Hb] and SaO₂ (Ie. CaO₂ decreases with anaemia)
 - (b) O₂ dissolved in plasma – Influenced by PaO₂ (Ie. CaO₂ decreases with hypoxaemia)

$$\text{CaO}_2 = (\text{PaO}_2 \times 0.03) + (1.34 \times [\text{Hb}] \times \text{SaO}_2)$$

- (2) Coronary blood flow (CBF):
 - CBF is 80 mL/min/100 g (or 200-250 mL/min assuming a 300 g heart) and accounts for 5% of CO at rest – This can increase by 3-4X (up to 400 mL/min/100g) in response to increasing myocardial O₂ demand or consumption

- CBF is determined by:
 - (a) Coronary perfusion pressure (CPP)
 - Majority of total CBF (80%) occurs during diastole due to extravascular compression of the coronary vessels during systole – This is more important for the LV as blood flow to it is intermittent (Ie. ceases during early systole) and mainly occurs during diastole; RV has a lower contractile pressure, hence blood flow to it does not cease during systole and is thus more pulsatile
 - Because of this, the driving pressure for CBF is determined by the “Aortic diastolic pressure” MINUS the “Extravascular compressive pressure” (larger of LV diastolic pressure or RA pressure)

$$\text{CPP} = \text{ADP} - (\text{larger of LVDP or RAP})$$

- Since LVDP and RAP are <<< ADP, CPP is $\approx$ ADP – Thus, ADP is clinically used to assess CPP (Nb. ADP cannot be easily accurately measured via non-invasively or invasively means)
- (b) Coronary vascular resistance
 - Coronary arteriole tone is generally high due to systolic compression of the vessels by the LV
 - Resistance can be controlled by:
 - (i) Local metabolic factors (MAIN factor) – Vasodilatory substances (Eg. H⁺, K⁺, CO₂, lactate, Etc.) produced from increased metabolic activity
 - (ii) Local myogenic (autoregulation) that keep CPP 60-180 mmHg

- (iii) ANS system – SNS fibres cause vasoconstriction (via α -receptors); PNS fibres cause vasodilation (via mAChR)

Myocardial O₂ demand and consumption:

- “Myocardial O₂ demand” is closely related to “Myocardial O₂ consumption”:
 - The former is related to “need”, whereas the latter is the “rate of O₂ consumed”
 - They can be equivalent when O₂ supply satisfies the O₂ demand – However, O₂ demand would EXCEED O₂ consumption if O₂ supply was limited, thereby creating an “O₂ debt”
- “Myocardial O₂ consumption” (MVO₂) is related to CBF and myocardial O₂ extraction by the “Fick Principle”:

$$MVO_2 = CBF \times (CaO_2 - CvO_2) = CBF \times (\text{Myocardial O}_2 \text{ extraction})$$

$$MVO_2 = (80 \text{ mL}/100\text{g}/\text{min}) \times (0.1 \text{ mL O}_2/\text{mL blood}) = 8 \text{ mL}/100\text{g}/\text{min}$$

MVO₂ can be measured by (i) ABG (for CaO₂), and (ii) Coronary venous sinus sampling (to measure CvO₂ and CBF)

- The myocardium is a highly oxidative organ, and it therefore has a very high O₂ demand and rate of O₂ consumption (MVO₂):

Condition	MVO ₂	Reason
Arrested	2 mL/100g/min (6 mL/min for 300 g heart)	Basal ATP use by membrane transport systems
At rest	8-10 mL/100g/min (21-27 mL/min for 300 g heart)	O ₂ consumption proportional to state of mechanical activity (I.e. degree of myocyte contraction and relaxation)
At exercise	70 mL/100g/min (210 mL/min for 300 g heart)	

- Myocardial O₂ demand and MVO₂ are determined by several factors:
 - (1) Major determinants
 - (a) Myocardial wall tension – Increased afterload results in increased MVO₂
 - (b) Contractility – Increased contractility leads to increased MVO₂
 - (c) Heart rate – Tachycardia increases MVO₂
 - (2) Minor factors:
 - (a) Basal energy metabolism (25% of total O₂ consumption – A large but constant amount of O₂ consumed)
 - (b) External work performed
 - (c) Energy for electrical activation (0.5-1%)
- A rise in myocardial O₂ demand due to changes in the aforementioned factors leads to a rise in MVO₂ (assuming that O₂ supply rises proportionally to meet O₂ demand). The rise in MVO₂ occurs as a result of:
 - (1) A rise in CBF (major factor):
 - CBF can increase by 4-5X (up to 400 mL/min/100g) due to metabolic autoregulation of the coronary arterioles – This is due to release of local vasodilatory substances from cardiac myocytes (Eg. CO₂, K⁺, lactate, H⁺, NO, adenosine, Etc.)
 - (2) A rise in myocardial O₂ extraction (CaO₂ – CvO₂) (minor factor)
 - Myocardial O₂ extraction ratio is already high at rest (55-65%; cf body average of 25%) because coronary blood supply is low relative to MVO₂
 - Thus, with increasing myocardial O₂ demands, the extraction ratio can only rise by 2X (rise up to 90% only)

Myocardial substrate metabolism:

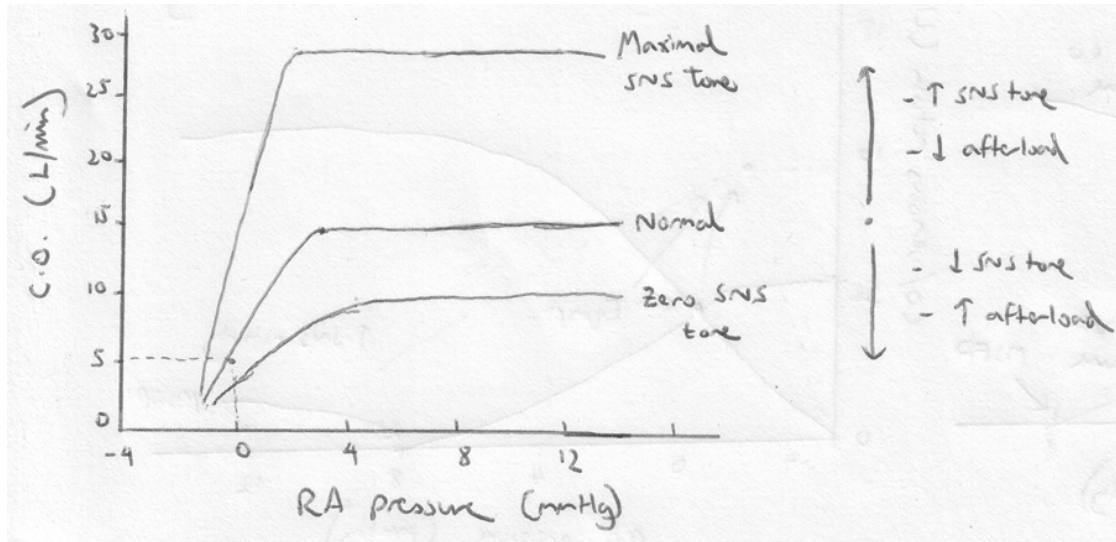
- Myocardium consumes several substrates (glucose, lactate, ketones and FAs), BUT generally the amount of each substrate used is directly related to its availability in blood:
 - (i) 40% of energy is derived from carbohydrates (glucose and lactate) – Nb. myocardium is sensitive to insulin, thus glucose uptake is enhanced in the presence of insulin
 - (ii) 60% of energy is derived from other substrates (mainly FAs)
- Normally, the myocardium undergoes oxidative metabolism of these substrates – With hypoxia, anaerobic glycolysis occurs BUT lactic acid produces is not readily removed, which leads to intracellular acidosis and myocyte death

Important to note → Efficiency of heart = 14-18 % (* Nb. This improves with exercise as C.O. ↑ considerably WITHOUT a proportional ↑ in O₂ consumption)

- (e) *To describe Guyton's cardiac output curves and to explain factors that affect them.*
- (f) *To describe and explain vascular function curves and to correlate these with the cardiac output curves.*

Cardiac Output Curve:

CO curve shows the effect of increases in RA pressure (independent variable) on the CO (dependent variable)



Features of the CO curve:

- With increasing RAP, there is a very steep upstroke such that small rises in RAP lead to large increases in CO
- A plateau is reached at higher RAP (> 4 mmHg) where CO is NOT dependent on RAP – The height of this plateau is dependent upon:
 - (i) Contractility state of the heart – With maximum SNS tone, CO can rise to 25-30 L/min at a RAP > 4 mmHg (cf. 15 L/min at a RAP > 4 mmHg in a resting state); it shifts the curve upwards
 - (ii) Afterload – Arteriolar vasoconstriction produces a rise in afterload that attenuates the CO at a given RAP; it shifts the curve downwards
 - Nb. Plateau height is NOT impacted by venous tone or blood volume (cf. vascular function curve)

Significance of CO curve:

- (1) Demonstrates the phenomenon of “heterometric autoregulation” (Frank-Starling mechanism), whereby CO is proportional to the preload (via RA pressure)
- (2) Shows that the normal heart has significant reserve pumping capacity (I.e. in the presence of raised RAP or +ve inotropes)
- (3) CO is determined by peripheral circulatory factors that regulate venous return (through RA pressure) – Moreover, venous return is substantially less than maximal cardiac pumping capacity, hence the heart can adjust its CO to match venous return via the Frank-Starling mechanism

Vascular Function (or Venous Return) Curve:

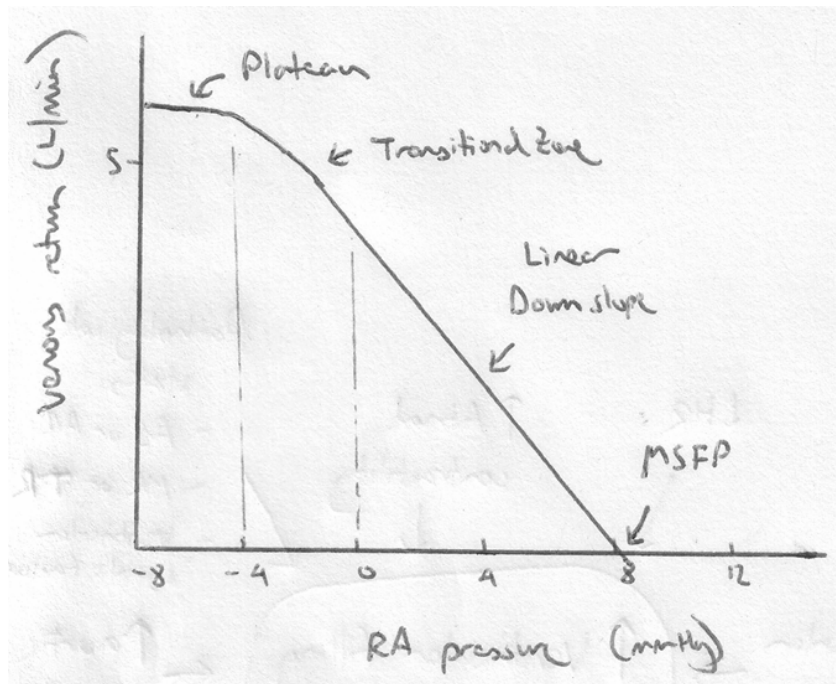
Definition of venous return:

- Venous return is the total blood flow in the vascular circuit that returns to the right side of the heart

- It is sum of all the individual tissue blood flow in the body – Blood flow to each tissue is determined by its metabolic needs (I.e. metabolic autoregulation of blood flow). Thus, increased tissue metabolic needs leads to a rise in tissue blood flow (I.e. by vasodilation of its supplying arteriole), which will lead to increased venous return
- Obeys Ohm's Law:

$$\text{Venous return} = \frac{(\text{Mean aortic pressure} - \text{RA pressure})}{\text{Total peripheral resistance}}$$

Guyton's vascular function (venous return) curve.



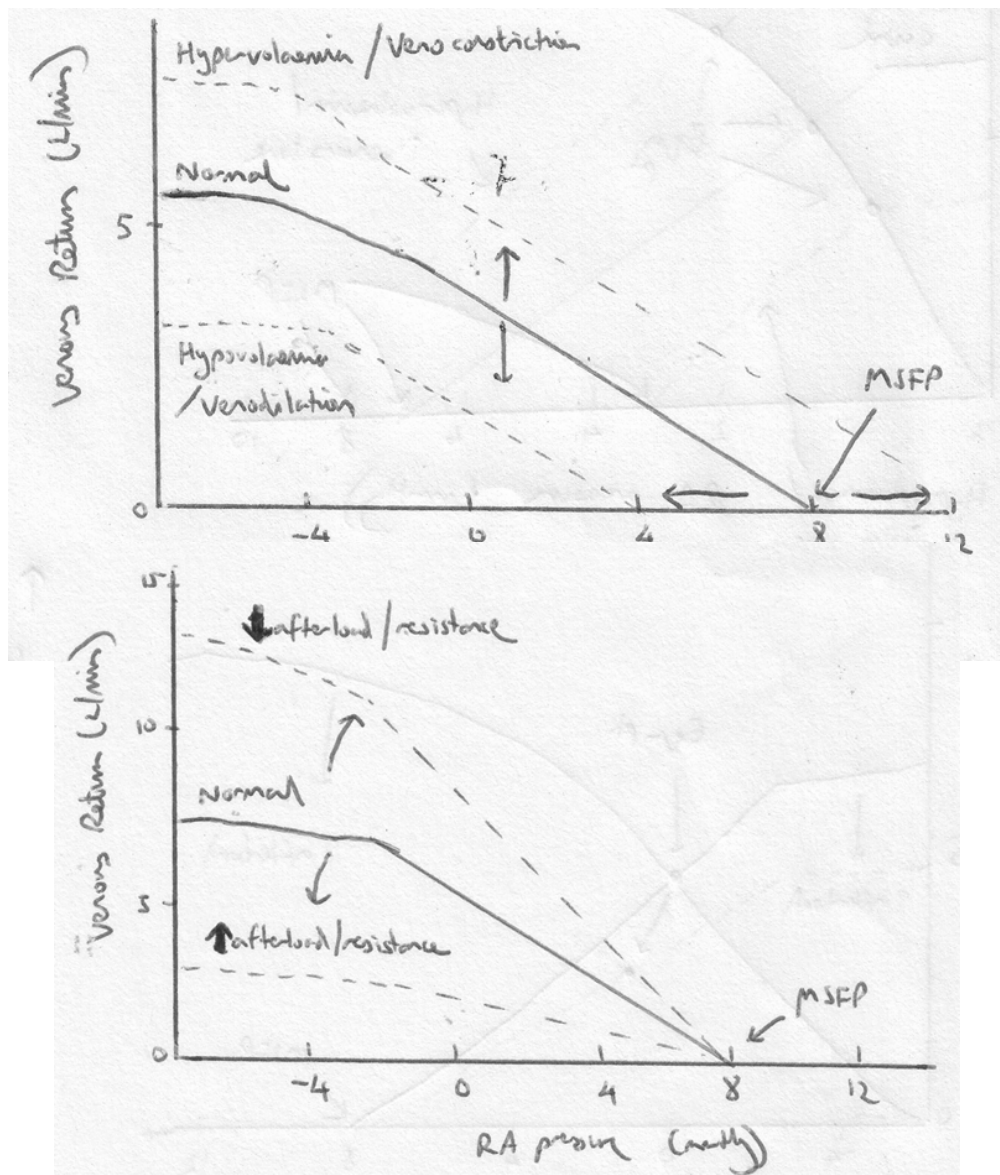
- Vascular function (venous return) curve shows the effect of increases in venous return or CO (independent variable) on RA pressure (dependent variable)
- Features of the curve:
 - o If RAP is raised to equal “Mean systemic filling pressure” (MSFP; ~ 7 mmHg), then there is a lack of a P_{GRADIENT} between the RA and venous system, therefore CO and venous return is zero (I.e. blood pools in the venous capacitance vessels)
 - o When RAP is between 0 mmHg and MSFP, then CO and venous return increase in a linear manner as RAP falls (up to 5 L/min when RAP is zero)
 - o When RAP is < 0 mmHg, CO and venous return plateaus at its maximum – This is because extrathoracic veins collapse (and act as Starling resistors) due to the negative intravenous pressures, thus limiting any further rise in venous return and CO
- This curve shows a linear relationship for venous return (for RAP between 0 and MSFP only; NOT when RAP < 0 mmHg):

$$\text{Venous return} = \frac{(\text{MSFP} - \text{RA pressure})}{\text{Resistance to venous return}} = \frac{P_{\text{GRADIENT for venous return}}}{\text{Resistance to venous return}}$$

Nb. $P_{\text{GRADIENT for venous return}} = 7 \text{ mmHg} - 1 \text{ mmHg} = \sim 6 \text{ mmHg}$

- The shape of this curve can be altered by the following factors:
 - o (1) Venous tone (venomotor tone)

- Ven constriction (Eg. due to SNS tone on venous capacitance vessels) increases MSFP, which shifts the curve upwards and rightwards (Ie. enhanced venous return at a given RAP)
- Venodilation (Eg. due to spinal block) decreases MSFP, which shifts the curve downwards and leftwards (Ie. decreased venous return at a given RAP)
- (2) Blood volume state
 - Hypervolaemia increases MSFP and produces an upward and rightward shift in the curve
 - Hypovolaemia decreases MSFP and produces a downward and leftward shift in the curve
- (3) Afterload (or arteriolar vascular resistance)
 - Changes in the dimension of the resistance vessels (arterioles) has a small effect on MSFP as only 2% of blood volume is in arterioles (cf. venous capacitance vessels) – Instead, it has an impact on “Resistance to venous return”
 - Decreased afterload (such as decreased SVR due to arteriolar vasodilation) increases the slope of the curve, thus increasing venous return (but keeping MSFP constant)
 - Increased afterload (such as increased SVR due to arteriolar vasoconstriction) decreases the slope of the curve, thus decreasing venous return (but keeping MSFP constant)



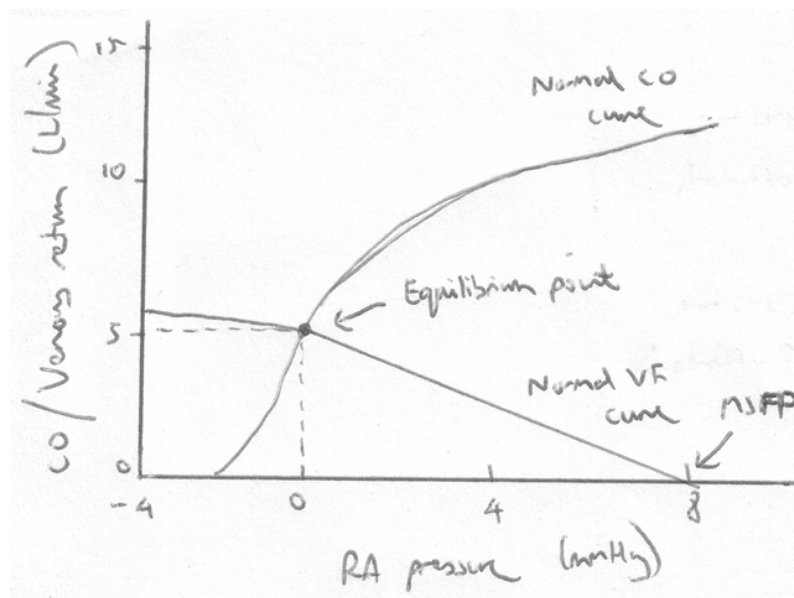
Factors that determine venous return back to the heart:

- Given the vascular function curve, the three variables that influence venous return are:
 - (1) Mean Systemic Filling pressure (MSFP)
 - If the heart suddenly stopped beating (and the situation was unaltered by CVS reflexes), MSFP would be the mean pressure that present in the systemic circulation at equilibrium – This pressure would be the average of all the pressures in different vessels (I.e. arteries and veins) weighted according to their relative compliances at equilibrium
 - MSFP is the main driving pressure moving blood back towards the RA – It is the MAIN factor determining venous return (and thus CO)
 - MSFP can be used to assess the degree of filling of systemic circulation:
 - It is normally 7 mmHg (0-20 mmHg), which indicates a degree of over-filling of the circulation
 - In the vascular function curve, MSFP is EQUAL to the RAP when venous return is zero
 - Two factors influence MSFP:
 - (i) Blood volume – MSFP increases with blood volume
 - (ii) Venomotor tone (venous capacitance) – MSFP rises with increased venomotor tone
 - (2) RA pressure
 - (3) Resistance to venous return
- Therefore, the factors that affect venous return influence one or more of the aforementioned variables:
 - (1) Blood volume
 - Blood volume is proportional to MSFP and thus venous return
 - (2) Venomotor tone
 - Increased venomotor tone (Eg. due to SNS activity) decreases vein compliance and capacity, which increases MSFP and venous return
 - Decreased venomotor tone (Eg. due to SAB) increases vein compliance and capacity, which decreases MSFP and venous return
 - This has a greater effect on venous return when (i) venous pressures are normal, and (ii) veins are circular (not collapsed and contain large volumes of blood)
 - (3) Venous valves
 - Veins have one-way valves that prevent retrograde flow
 - (4) Skeletal muscle pump
 - Alternating contraction and relaxation of limb skeletal muscle forces blood out of the veins towards the heart (thus, increasing MSFP) – During contraction, veins compress to expel blood towards the heart, then during relaxation, veins distend and fill with blood
 - With exercise, this pump function enhances net venous return
 - (5) Respiratory pump
 - During inspiration, venous return is increased due to (i) fall in RAP (associated with fall in $P_{\text{INTRAPLEURAL}}$), and (ii) increased IAP (due to diaphragmatic contraction)
 - During expiration, the effects are reversed
 - Note that if RAP is < 0 mmHg, the respiratory pump will NOT have any effect on venous return as the thoracic veins would have collapsed at subatmospheric pressures
 - (6) Posture
 - Posture has an effect on blood pooling in the venous capacitance system – When going from supine to erect, there is reduced venous return due to venous pooling in the lower extremities
 - Normally, there is reflex vasoconstriction to prevent this BUT this reflex is delayed and less effective in the elderly

- (7) Effect of ventricular contraction and relaxation
 - During rapid ejection phase of ventricular systole, atrial pressure falls sharply (to zero or –ve values) as the ventricle contraction pulls the atrioventricular fibrous ring downwards and increases the atrial volume – This causes net blood flow into atria and increases venous return
 - During early diastole, ventricles fill rapidly causing both ventricular and atrial pressures to decline – This facilitate blood flow into atria and increases venous return
- (8) Intrapericardial pressure
 - Increased intrapericardial pressure (Eg. tamponade) can increase RAP, thus impeding venous return
- (9) Afterload
 - Changes in the dimension of the resistance vessels (arterioles) has a small effect on MSFP as only 2% of blood volume is in arterioles (cf. venous capacitance vessels) – Instead, it has an impact on “Resistance to venous return”
 - Decreased afterload (such as decreased SVR due to arteriolar vasodilation) decreases resistance to venous return, thus increasing venous return
 - Increased afterload (such as increased SVR due to arteriolar vasoconstriction) increases the resistance to venous return, thus decreasing venous return

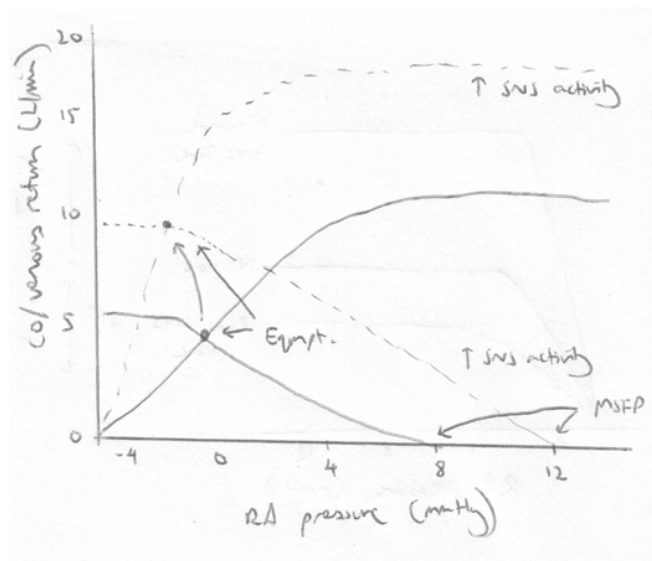
Relationship between Cardiac Output and Vascular Function Curves:

- To maintain a stable circulation, an equilibrium between CO and venous return must exist – In other words, these two variables must be equal and cannot differ more than a few heartbeats before a new equilibrium state is reached
- This equilibrium can be demonstrated by superimposing the CO and Vascular function curves:

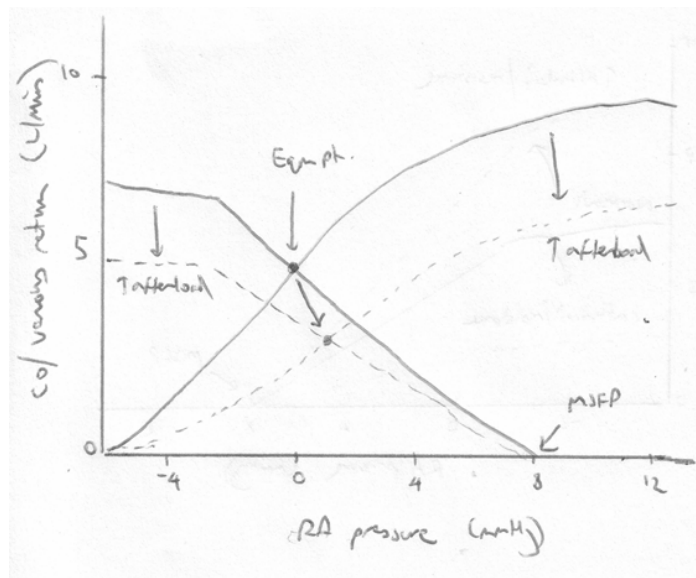


- The point of intersection of these two curves produces an “Equilibrium Point”:
 - This point defines the CO and RA pressures at which the cardiovascular system operates – This is normally a RA pressure of 0 mmHg and a CO or venous return of 5 L/min
 - Factors that shift this “Equilibrium Point” are the factors that alter the CO and vascular function curves:
 - (1) Contractility state
 - (2) Afterload (arteriolar resistance to venous return)

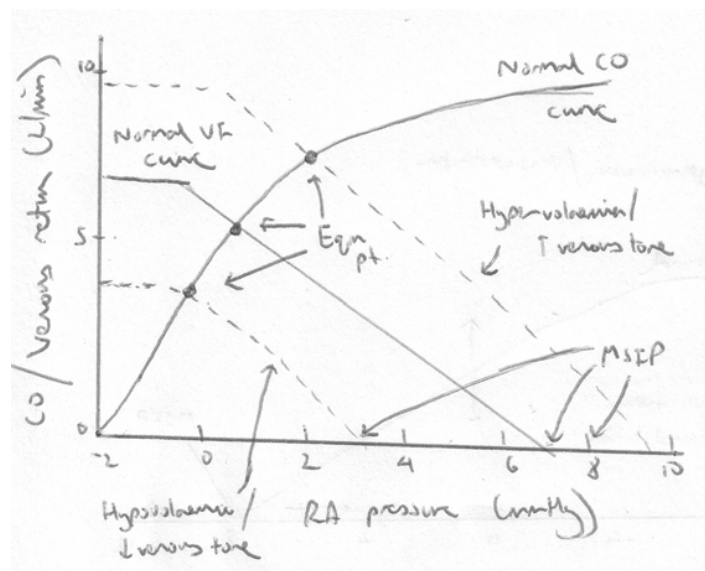
- (3) Blood volume
- (4) Venomotor tone
- For example:
 - Increased contractility state (Eg. SNS tone)



- Increased afterload



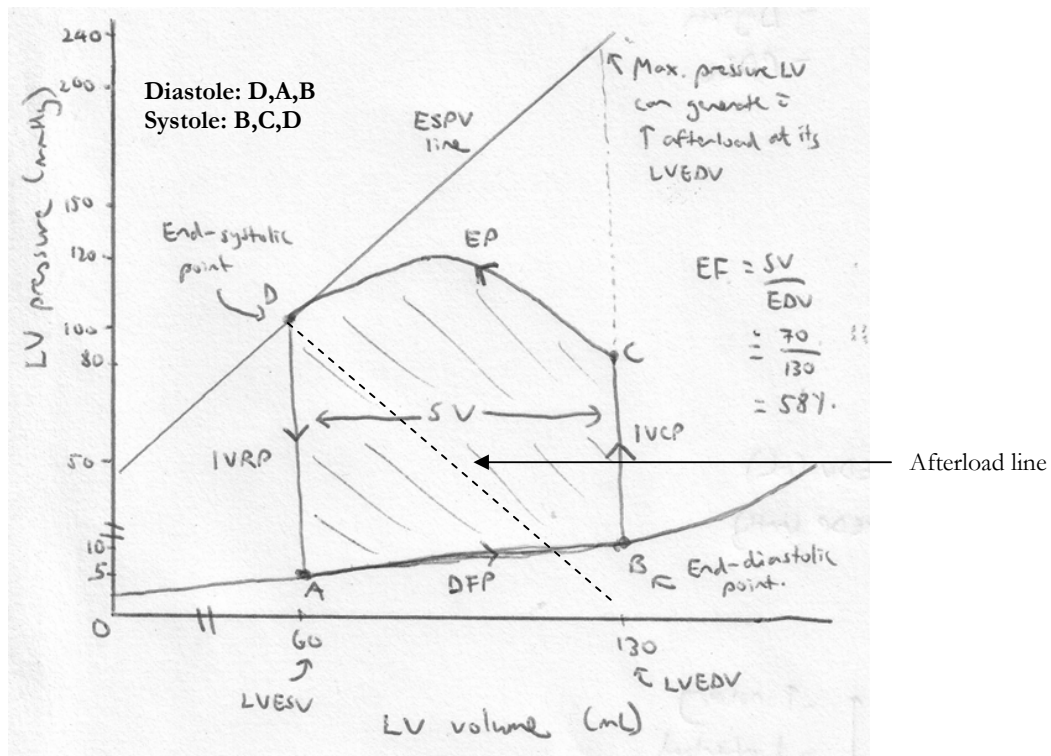
- Changes in blood volume or venomotor tone



- (g) *To describe the pressure-volume relationships of the ventricles and their clinical applications.*

Pressure-volume relationship of the ventricles:

P-V relationship of the LV:



A-B: Ventricular filling phase (diastole)

- LV volume rises from 60 mL at end of systole to EDV of 130 mL
- LV pressure rises from 5 mmHg to 10 mmHg at the “end-diastolic point” (point B)

B-C: Isovolumetric ventricular contraction phase (start of systole)

- There is a rapid rise in LV pressure – It exceeds LA pressures (~ 5 mmHg) causing the mitral valve to close (at point B). When it reaches 80 mmHg, LV pressure exceeds the aortic root pressure causing the aortic valve to open (at point C)
- LV volume remains the same at 130 mL during this phase

C-D: Ejection phase (systole)

- LV contracts and ejects the SV of 70 mL against the afterload of increasing aortic pressure. LV volume decrease from 130 mL to 60 mL at the end of systole (aka. ESV)
- LV pressure rises to 120 mmHg and then falls to 100 mmHg at the end of systole (or “end-systolic point”; point D). At this point, LV pressure is less than aortic root pressure, thereby causing the aortic valve to close again

D-E: Isovolumetric ventricular relaxation phase (start of diastole)

- Ventricular pressure falls from the “end-systolic point” LV pressure of 100 mmHg to less than LA pressure (~ 5 mmHg) towards the end of this phase (at point A). When this happens, the mitral valve re-opens

Important information that can be derived from the LV pressure-volume loop:

- (1) Stroke volume (SV) – This is the difference of LVESV from LVEDV (or 130 mL – 60 mL = 70 mL)
- (2) Ejection fraction – Provides an index of LV systolic function (See below)

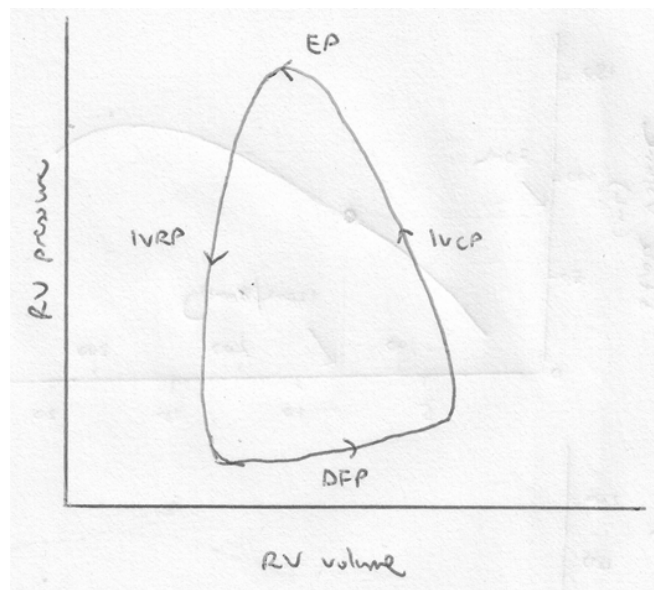
$$EF = \frac{(LVEDV - LVESV)}{LVEDV} = \frac{SV}{LVEDV} \approx \frac{(130 \text{ mL} - 60 \text{ mL})}{130 \text{ mL}} \approx 54\%$$

- (3) Measure of preload – LVEDV is the BEST index of preload on the curve
- (4) Measure of afterload

- “Afterload line” is an index of afterload on the P-V curve
- It is formed by a straight line connecting the “end-systolic point” with the LVEDV on the x-axis – A larger slope means increased afterload
- (5) Measure of contractility
 - “End-systolic pressure volume (ESPV) line” is an index of contractility on the P-V curve
 - It is formed by a straight line extending from the “end-systolic point”. Extrapolation of this line to the x-axis reveals the LV volume if the LV pressure was zero (V_0) – A larger slope means increased contractility
- (6) Measure of elastance (or stiffness) and compliance (or distensibility) of the LV (See ventricular diastolic function below)
- (7) Peak LV pressure that can be generated
 - Point at which aortic valve opens is normally at a much lower pressure than the maximum pressure the ventricles can generate at its normal EDV (I.e. in face of an increased afterload)
 - Note that a rise in afterload can result in an increase in ventricular pressures up to the “Maximal isometric point”
- (8) Measure of cardiac workload (See below)
 - (a) Total mechanical energy (or stroke work)
 - (b) Heat generated by the heart during contraction
 - (c) “Diastolic work”

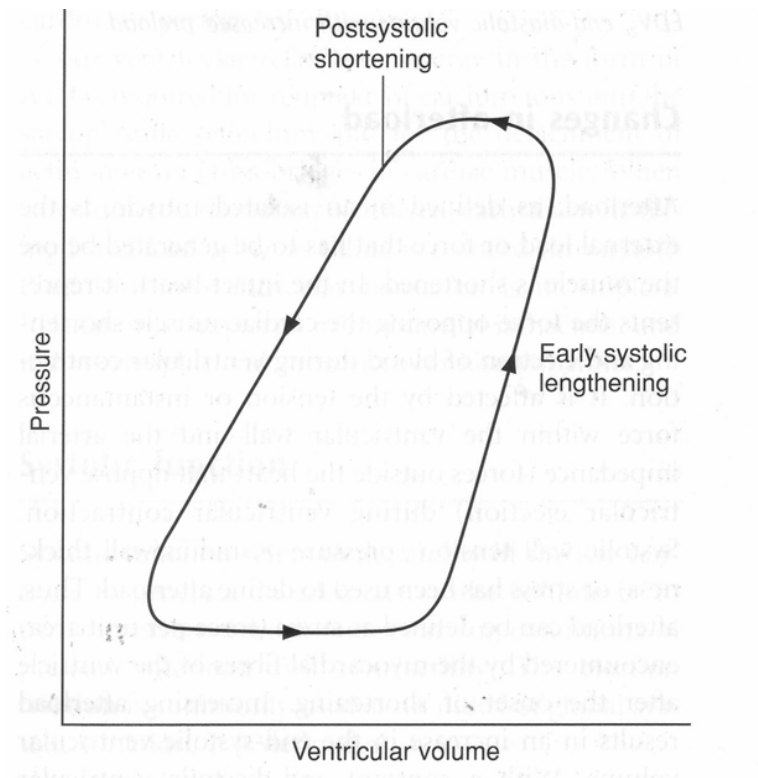
Difference in P-V loop between LV and RV:

- LV P-V loop shown above is “rectangular” (See above)
- RV P-V loop is more “triangular” (See below) – This is because RV contraction is NOT synchronous (unlike the LV), as it starts in the inflow tract and in a peristaltic manner reaches the outflow tract after a 50 msec delay



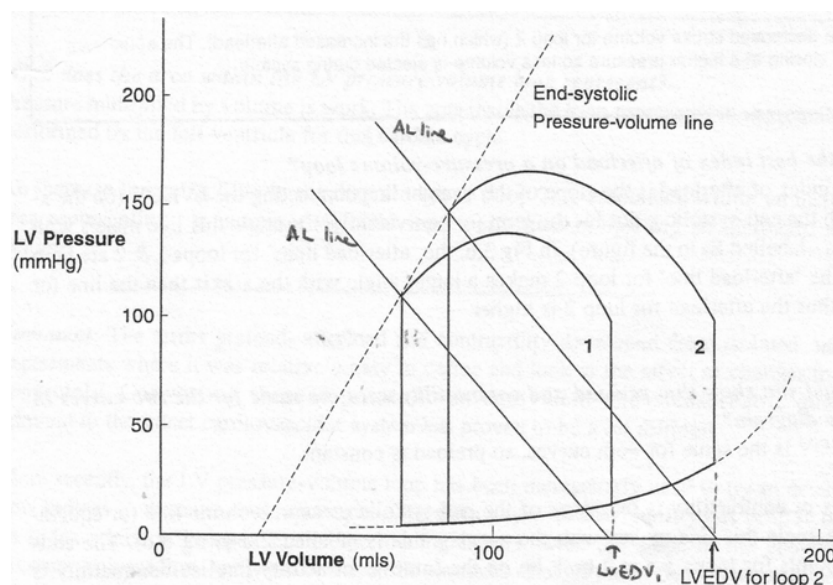
Effect of cardiac ischaemia on the P-V loop:

- This will cause the loop to lean towards the right due to:
 - (i) Systolic lengthening of ventricular muscle during IVCP – Due to displacement (or bulging) or ischaemic muscle with contraction of normal ventricular muscles
 - (ii) Postsystolic shortening of ventricular muscle during IVRP – Due to active shortening of ventricular muscle or elastic recoil of the ventricle with profound ischaemia

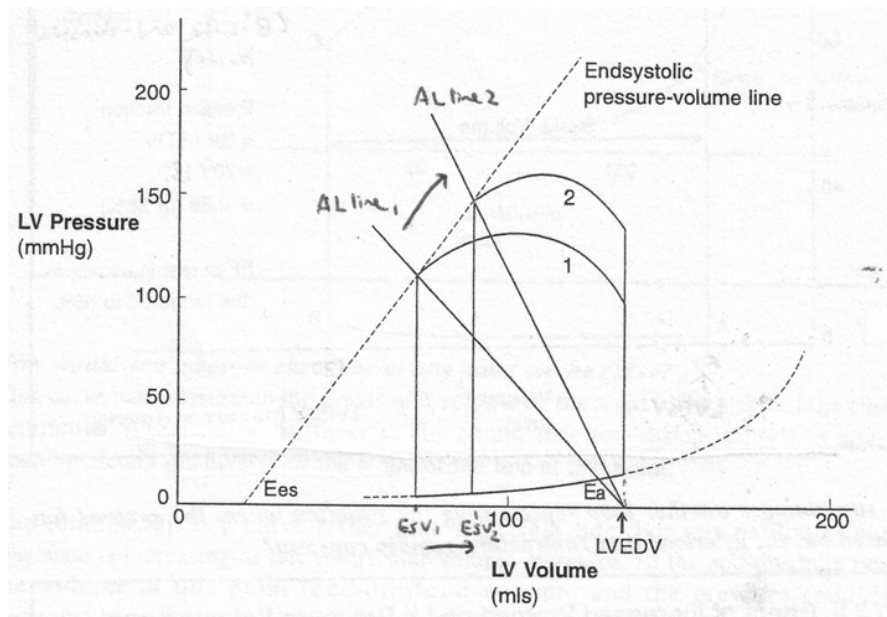


Factors influencing the pressure-volume relationship of the left ventricle:

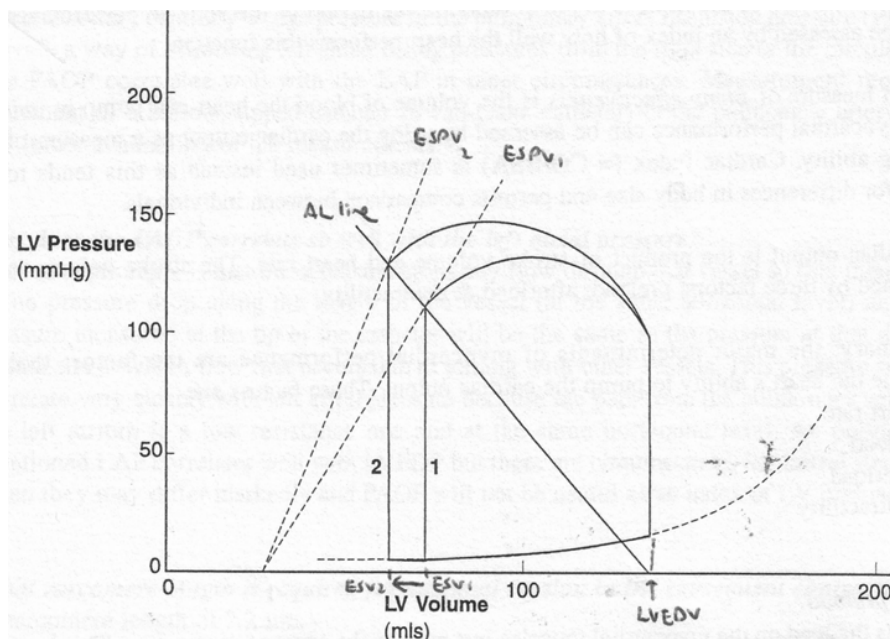
- (1) Changes in preload:
 - Increases in preload will result in increased LVEDV due to increased ventricular filling. This will lead to a rise in SV due to the Frank-Starling mechanism, and a slight rise in ESV as well assuming a constant afterload (parallel afterload lines) and contractility (same ESPV line)



- Decreases in preload will produce opposite effects (decreased LVEDV, fall in SV and a slight fall in ESV assuming a constant afterload and contractility)
- (2) Changes in afterload:
 - Increases in afterload produce a greater slope in the afterload line, which lead to a rise in ESV and a net decrease in SV (assuming preload and contractility are constant (I.e. same LVEDV and same ESPV line))



- Decreases in afterload produce opposite effects (fall in ESV and net increase in SV, assuming constant preload and contractility)
- (3) Changes in contractility:
 - Increases in contractility (I.e. due to +ve inotrope) produce an increased slope of the ESPV line which leads to a fall in ESV and a net increase in SV (assuming preload and afterload are constant (I.e. same LVEDV and same afterload line))

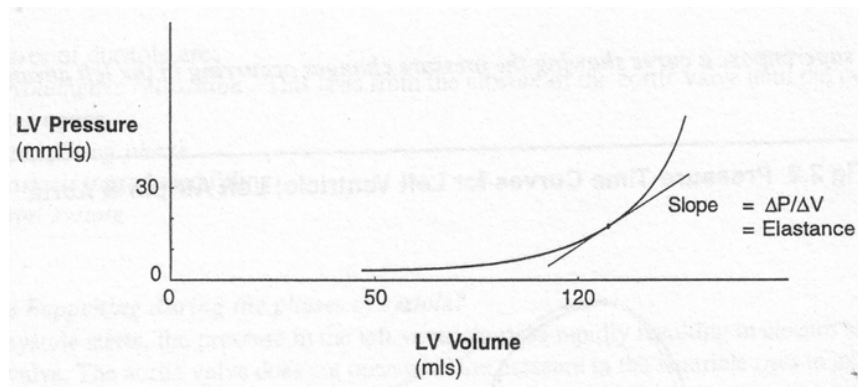


- (i) Depression of the ESPV slope WITHOUT a change in V_o
- (ii) Parallel shift of the ESPV line causing a rise in V_o WITHOUT a change in the slope
- Note that both these effects will lead to a rise in ESV and a net decrease in SV assuming a constant preload and afterload

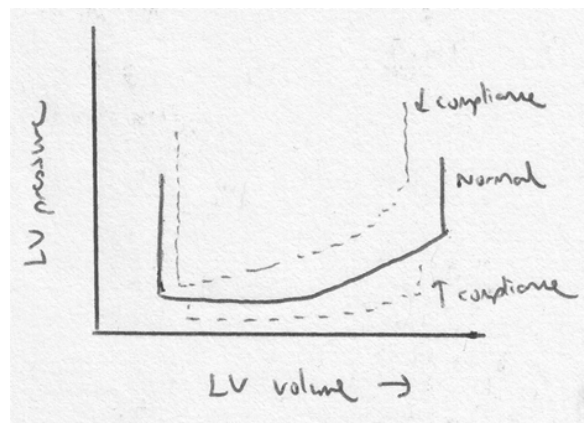
Ventricular diastolic function:

- Reflects the passive properties or stiffness of the ventricular muscles
- Gauged by the P-V relationship at the end of diastole
- Ventricular diastolic function is dependent on:
 - (1) Ventricular diastolic compliance

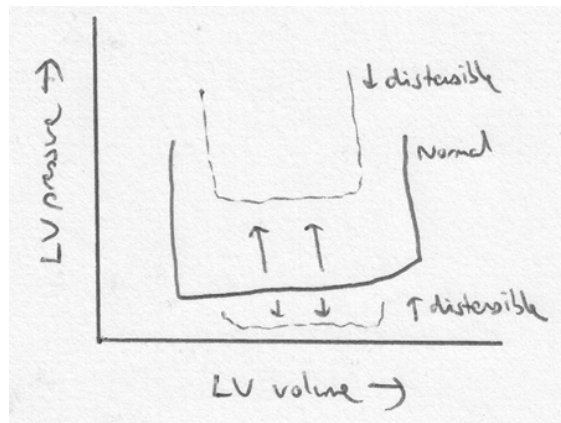
- The slope of the diastolic P-V relationship ($\Delta P/\Delta V$) is a measure of ventricular elastance (or stiffness) – The inverse of this is a measure of ventricular compliance or (distensibility) ($\Delta V/\Delta P$)



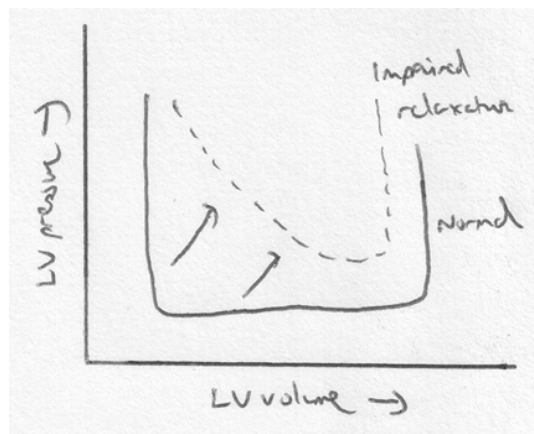
- The diastolic P-V relationship is non-linear (Ie. it is curved):
 - At physiological limits (LVEDV < 120 mL), the curve is relatively flat (Ie. shallow slope) – Thus, at these EDVs the LV is very compliant (Ie. LV volume increases without much change in pressure)
 - However, with excessive LV filling (Ie. LVEDV > 120 mL), the curve rises steeply – Thus, LV becomes very stiff (Ie. LV volume increases only with a large change in pressure), thereby preventing “overfilling” of the LV
- Ventricular compliance is altered by diseases states:
 - (i) Reduced compliance (or higher slope of diastolic P-V relationship) is caused by LVH or restrictive cardiomyopathy
 - (ii) Increased compliance (or shallower slope of diastolic P-V relationship) is caused by dilated cardiomyopathy



- (2) Ventricular distensibility:
 - Conditions that decrease ventricular distensibility (Eg. MI, pericardial effusion, constrictive pericarditis) produce a parallel upward shift of the diastolic P-V relationship – This means that a higher diastolic pressure is observed at a given ventricular volume



- (3) Ventricular relaxation:
 - Energy is needed for ventricular relaxation to occur (I.e. ATP is required for reuptake of Ca^{2+} ions into the SR and for detachment of actin-myosin cross-bridges)
 - Impaired ventricular relaxation (Eg. MI, HOCM) leads to (i) a delay in isovolumetric ventricular relaxation (which reduces early diastolic filling), and (ii) reduced ventricular filling throughout entire diastole



Ventricular systolic function:

- Reflects the active contractile properties of cardiac muscle, which influences the ability of the LV to generate adequate stroke volume or to perform external work under varying conditions of preload, afterload or contractility
- Gauged by the P-V relationship at end of systole
- Indices of ventricular systolic function:
 - (i) "Ejection fraction" is commonly used:

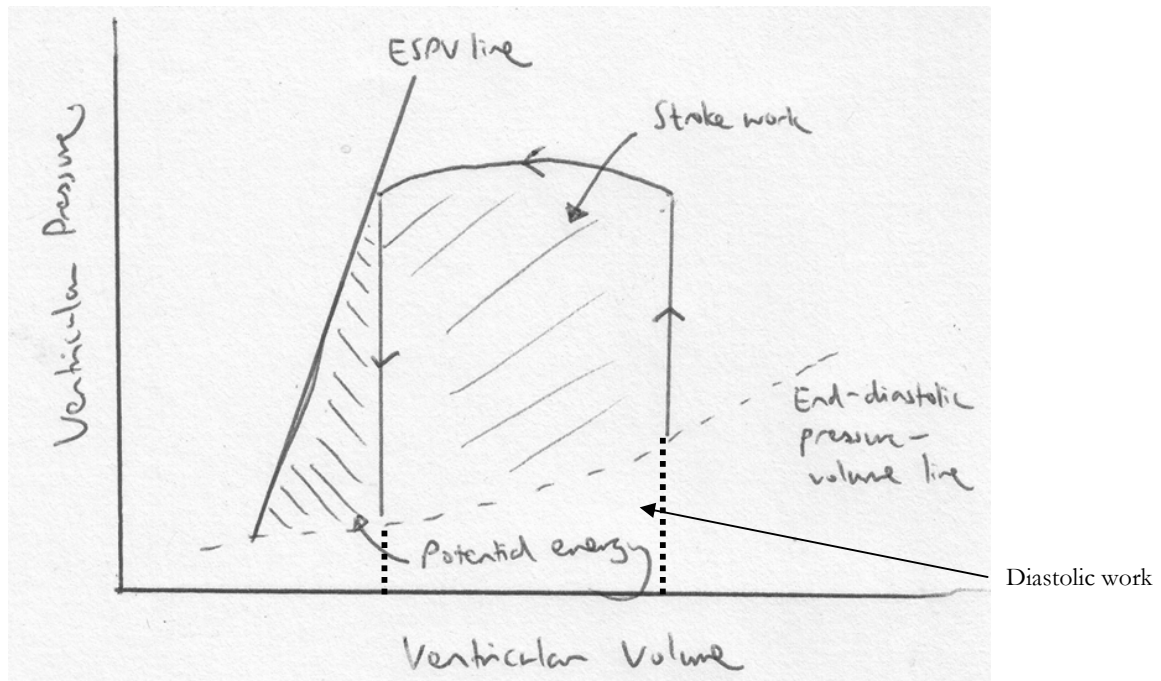
$$EF = \frac{LVEDV - LVESV}{LVEDV} = \frac{SV}{LVEDV} \approx \frac{(130 \text{ mL} - 60 \text{ mL})}{130 \text{ mL}} \approx 58\%$$

- EF is influenced by:
 - (i) Preload – EF increases with increased preload (through a rise in LVEDV and SV)
 - (ii) Afterload – EF increases with decreased afterload (through decreased LVESV and a rise in SV)
 - (iii) Contractility – EF increases with increased contractility (through decreased LVESV and a rise in SV)
- (ii) Gradient of the ESPV line – A measure of ventricular contractility that is independent of preload and afterload

- (iii) Qualitative assessment of regional LV wall motion (by LV gram or ECHO) – Normal areas of myocardium show concentric inward movement with systole. Ischaemic myocardium are hypokinetic with reduced concentric inward motion or akinetic with no wall motion (if there is fibrous scar tissue present). Unviable myocardium produce dyskinetic areas with paradoxical bulging during systole

Area of the P-V loop: Index of mechanical energy and work

- Analysis of P-V relationships of both ventricles provide a measure of the workload of heart



- “Pressure-volume area” (PVA) is the sum of the:
 - (1) Total mechanical energy (or stroke work)
 - This is the external work done by the ventricle for that cardiac cycle
 - It is measured by the area within the ventricular P-V loop
 - (2) Heat generated by the heart during contraction
 - This represents the potential energy generated during the cardiac cycle, which occurs during isovolumetric ventricular contraction when ventricular pressures rise but blood is not ejected (I.e. no external work is done) – This potential energy is later converted to heat during diastole
 - It is measured by the triangular area formed by – ESPV line, end-diastolic P-V line, line representing isovolumetric ventricular relaxation
- PVA correlates well with the amount of O_2 consumed by the myocardium during a single contraction (or for that cardiac cycle):
 - When the PVA is extrapolated to zero ventricular pressure, myocardial O_2 consumption is still present – This represents the basal consumption needed to keep the myocardium alive in absence of pressure development
 - When pressure development occurs and ventricular pressure rises, activation energy is required to run the biochemical processes associated with excitation-contraction coupling
- “Diastolic work”
 - This represents the stored energy within the ventricular muscle from the previous cardiac cycle – This energy is derived from work done by blood to stretch the myocardium:
 - It is measured from the area of the curve below the diastolic P-V line

(h) **To integrate the factors that determine cardiac output.**

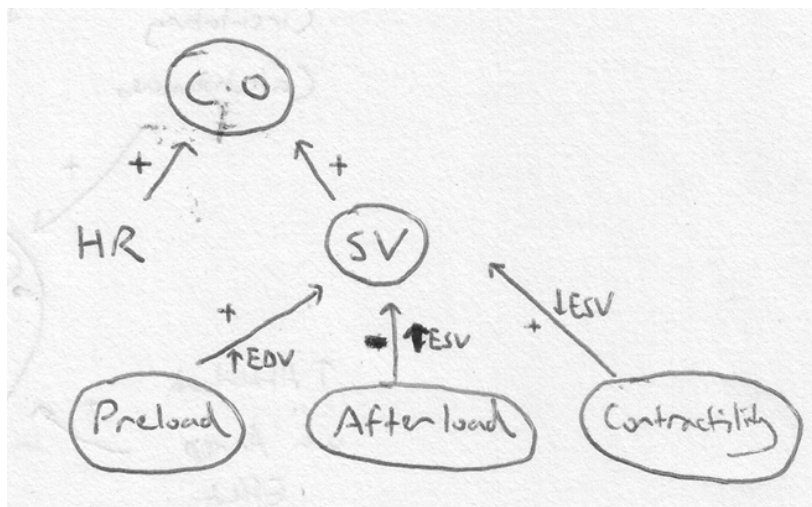
Overview of cardiac output:

- C.O. is the volume of blood ejected from the ventricle per minute

$$\text{C.O.} = \text{HR} \times \text{SV}$$

- 5 L/min at rest (70 mL of blood ejected/beat at 70 bpm), but can rise to 25-30 L/min with exercise (majority of it going to skeletal muscle – up to 20L/min!)
- Used to assess myocardial performance as it gauges the heart's pumping ability to supply blood to the tissues of the body
- “Cardiac index” (CI) – This allows C.O. to be standardised to BSA to account for differences in body size (measured in L/min/m²)

Factors that determine cardiac output:



(1) Ventricular stroke volume:

- “Stroke volume” is the volume of blood ejected with each contraction (SV ~ 70 mL/beat) – It is determined by the difference of (i) End-systolic volume (residual blood volume remaining in the ventricle after ejection; ~ 50 mL) from (ii) End-diastolic volume (filled ventricular volume prior to contraction: ~120 mL)

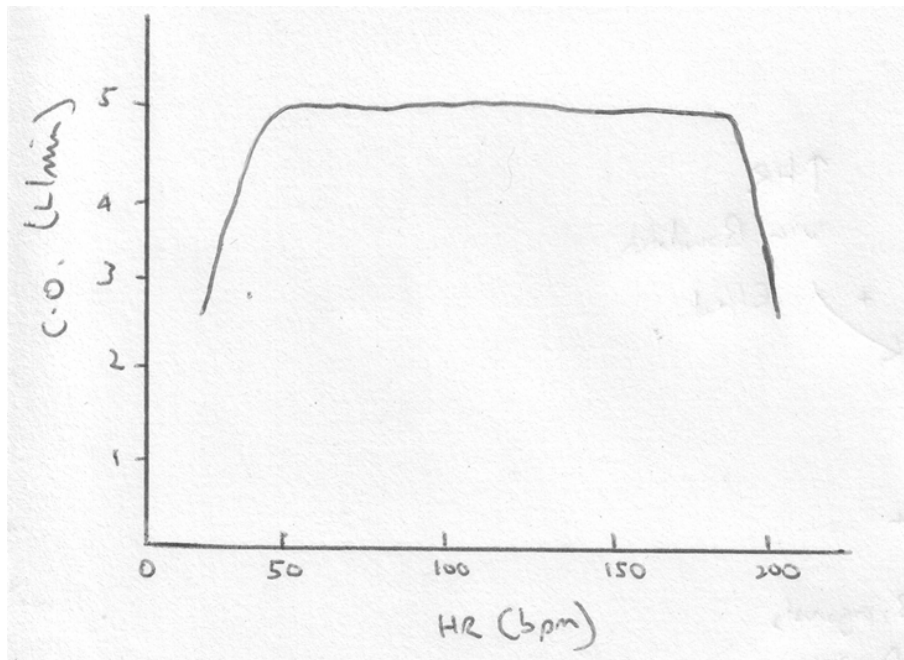
$$\text{SV} = \text{EDV} - \text{ESV}$$

- Factors that influence SV include:
 - (a) Preload
 - Changes in preload affect SV through the Frank-Starling mechanism – Increases in preload (Eg. venous return) leads to a rise in ventricular filling and EDV, which causes increased muscle fibre stretching, thus escalating the force of ventricular contraction and increasing SV
 - (b) Afterload
 - Changes in afterload affect the ability of ventricle to eject blood into the aorta – Increases in afterload (Eg. AS or HTN) leads to a rise in ESV, which decreases SV
 - Note – SV is NOT strongly influenced by afterload in a normal and healthy ventricle as the secondary rise in preload and Frank-Starling mechanism normalises it (I.e. SV is mainly decreased with heart failure)
 - (c) Contractility

- Changes in ventricular inotropy alter the rate of ventricular pressure developed ($[dp/dt]_{MAX}$), thus affecting ESV and SV – Increases in inotropy (Eg. SNS stimulation) leads to a fall in ESV, which results in increased SV
- Note that the changes in EDV and ESV on SV are NOT independent:
 - While the 1° effect of a change in preload, afterload or contractility may be on either EDV or ESV, 2° changes can occur that can partially compensate for the initial change in SV
 - For example: Increased afterload reduces SV, but this can be compensated for by a 2° rise in preload via the Frank-Starling mechanism, and increased inotropy via Anrep effect

(2) Heart rate:

- C.O. is RATE-INDEPENDENT – It is NOT affected by 1° changes in HR over a wide range (40-50 bpm to 170-180 bpm)
- At very fast HR ($> 170-180$ bpm), the short diastolic time compromises ventricular filling such that C.O. will fall with a further increase in HR
- At low HR (40-50 bpm), the prolonged diastolic time ensures LVEDV and SV reaches its maximum. HOWEVER, any further decrease in HR will then be associated with a fall in SV and C.O.



Relationship between cardiac output and venous return:

- The heart acts as a “demand pump”, meaning that it pumps blood around the body according to the demands of the tissues – The tissues “signal” their flow requirements to the heart by altering venous return
- Venous return is defined as the total blood flow in the circulation that returns to the right side of the heart. It is the sum of all the individual tissue blood flows – this is influenced by the metabolic demands of the tissue via metabolic autoregulation, such that increased tissue demand (Eg. exercising) leads to increased tissue blood flow (I.e. via vasodilation 2° local metabolic mediators) and thus increased venous return
- Cardiac output can be seen as the total blood flow leaving the left side of the heart into the circulation. Since the vascular circuit is a closed system, cardiac output MUST equal venous return (although this may vary briefly due to the pulsatile (discontinuous) nature of flow at some points in the circulation)
- Matching of C.O. and venous return occurs via:
 - (1) Heterometric autoregulation

- This causes C.O. to rapidly match acute changes in venous return, and to match C.O. between the LV and RV
- Involves:
 - (i) Maintaining the same SV via Frank-Starling mechanism (increased preload causes increased contractile force, and a rise in SV) and by reflexly increasing the HR (due to stretching of the SA node)
 - (ii) Maintaining the same rate of contraction between the LV and RV (both ventricles share a conducting system that ensures they contract at the same rate)
- (2) Homeometric autoregulation
 - Involves increased force of ventricular contraction due to an increase in contractility (independent of preload and afterload) 2° a rise in intracellular free Ca^{2+} in myocardial cells
 - Unlike heterometric autoregulation, there is no ventricular distension which is associated with increased afterload (as per Law of LaPlace)
- Note that 1° changes in HR or SV (Ie. increase in HR due to pacing or drugs) will NOT affect C.O. if there is a lack of increased demands from the tissue (Ie. SV will reflexly decrease to maintain C.O.)

II. ELECTRICAL PROPERTIES OF THE HEART

- (a) *To explain the ionic basis of spontaneous electrical activity of cardiac muscle cells (automaticity).*
- (b) *To describe the normal and abnormal processes of cardiac excitation.*
- (c) *To explain the physiological basis of the electrocardiograph in normal and common pathological states.*
- (d) *To describe the factors that may influence cardiac electrical activity.*
- (e) *To describe and explain the mechanical events of the cardiac cycle and correlated this with electrical ionic events.*

(A) Cardiac Action Potential:

Remember these concepts:

(1) *Ionic basis of cell potentials:*

- Various phases of an AP are a/w changes in permeability of cell membrane to Na^+ , Ca^{2+} , K^+ due to opening/closing of respective ion channel $\rightarrow$ causes a net flux of ions across the membrane according to its electrical and chemical gradients

(2) *Resting membrane potential (RMP):*

- (a) RMP is mainly due to the “equilibrium (or Nernst) potential” of K^+ $\rightarrow$ this is b/c the resting cell membrane is largely permeable to K^+ (cf. Na^+ and Ca^{2+}), which results in a net K^+ diffusion out of cell along its opposing electrical and chemical gradients $\rightarrow$ develop a $-ve$ electrical potential in interior of cell

“Nernst equation” $\rightarrow$ determines electrostatic potential that would exist across the cell of a given ion (K^+) when the chemical and electrical gradients are at equilibrium

$$E_K = -61.5 \log ([\text{K}^+]_i / [\text{K}^+]_o)$$

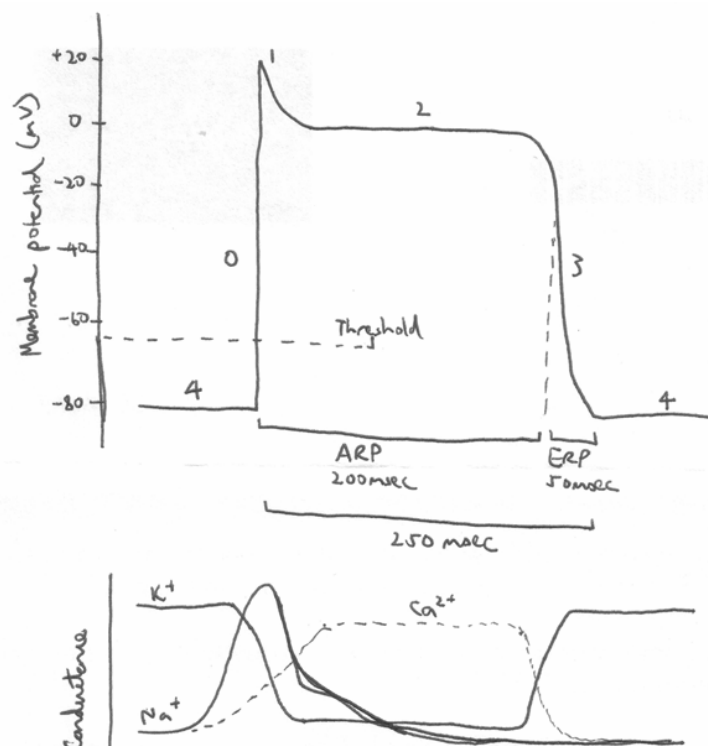
- (b) RMP is slightly more $+ve$ than Nernst potential of K^+ due to small inward Na^+ current $\rightarrow$ caused by low membrane permeability to Na^+
- (c) RMP is also the result of (i) Gibbs-Donnan effect and (ii) Na^+/K^+ ATPase

(3) *Threshold potential* $\rightarrow$ “critical” membrane potential at which an self-propagated AP is generated

There are two types of cardiac APs:

(1) “Fast response” type

Location: Atrial cells, ventricular cells and Purkinje fibres



Phases:

Phase	Process	Ionic basis
0	“Rapid depolarisation” – Cell is rapidly depolarised from RMP (-90 mV) up to “threshold” (-65 mV) → produces a large amplitude AP	- (1) Fast VG- Na^+ channels open → ↑ membrane Na^+ permeability → ↑ Na^+ influx - (2) VG- K^+ channels close → ↓ membrane K^+ permeability → ↓ K^+ efflux
1	“Spike” – Cell membrane potential reaches peak of +20 mV → then partially repolarises	Rapid closure of fast-VG Na^+ channels → rapid ↓ membrane Na^+ permeability → ↓ Na^+ influx
2	“Plateau” – Cell membrane maintains depolarisation	- (1) L-type VG- Ca^{2+} channels open → ↑ membrane Ca^{2+} permeability → ↑ Ca^{2+} influx - (2) Gradual closure of fast VG Na^+ channels → gradual ↓ membrane Na^+ permeability → ↓ Na^+ influx
3	“Repolarisation” – Cell membrane repolarises to RMP	Membrane permeabilities of Na^+ , Ca^{2+} and K^+ return to resting state: - (1) L-type VG- Ca^{2+} channels close - (2) Fast VG- Na^{2+} channel close - (3) VG- K^+ channels reopen
4	“Resting potential” – Membrane potential returns to a “stable” RMP (-90 mV)	- (1) Resumption of ↑ membrane K^+ permeability (and K^+ efflux) → due to opening of VG- K^+ channels - (2) Na^+/K^+ ATPase → 3x Na^+ influx and 2x K^+ efflux - (3) $\text{Na}^+/\text{Ca}^{2+}$ antiport → 3x Na^+ influx and 1x Ca^{2+} efflux - (4) Ca^{2+} ATPase → Ca^{2+} efflux

Duration of AP: 250 msec → consists of 2 phases:

- (a) Absolute refractory period → first 200 msec (phase 0 to 1st part of phase 3)
 - o Cardiac cell is “inexcitable” during this period → b/c fast VG- Na^+ channels are still open
- (b) Relative refractory period → other 50 msec (last part of phase 3)
 - o Only a supramaximal stimulus can generate an AP → b/c some fast VG- Na^+ channels have reset and can be reopened

Note – During the RRP, a supramaximal stimulus generates an AP with a (i) slower rate of depolarisation (phase 0), (ii) smaller amplitude and (iii) shorter than normal AP (ie. weaker contraction and slower conduction velocity) → the later the stimulus during the RRP, the greater the rate of depolarisation, amplitude and duration of AP (Ie. stronger contraction and faster conduction velocity), until RMP in phase 4 is reached and a normal AP can be generated

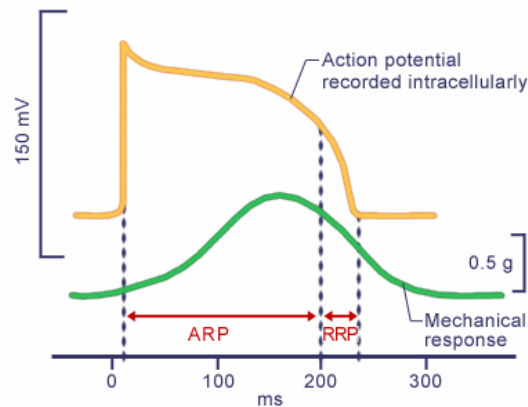


Conduction velocity: Fast (1 m/s in atria; 4 m/s in Purkinje fibres)

Important to note – It is IMPOSSIBLE to summate contractions or tetanise cardiac muscle because (I.e. cardiac muscle is fully relaxed before it can contract again):

- (1) Duration of cardiac muscle contractile response (300 msec) is as long as the duration of the cardiac muscle AP (250 msec)
- (2) Cardiac muscle AP has a LONG refractory period → cardiac muscle is in absolute refractory period most of the time and cannot be re-excited

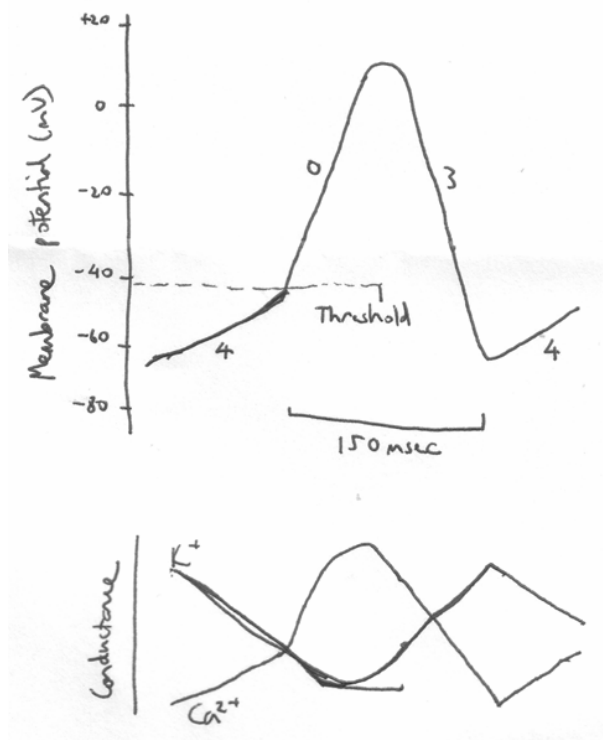
Significance – This prevents the ventricles from being activated again before they have had time to relax and fill with blood after they have contracted and ejected blood



(2) “Slow response” type

Location: SA and AV nodal cells

Note – SA and AV nodal cells have the same ionic basis BUT the rate of depolarisation of “pacemaker potential” (phase 4) is slower in the AV node



Phases:

Phase	Process	Ionic basis
4	“Pacemaker potential” or “Pre-potential” – RMP is “unstable” (b/t -70 to -40 mV) and spontaneously depolarises to “threshold” (-40 mV) → produce AP	- (1) ↓ membrane K^+ permeability → ↓ K^+ efflux - (2) Opening of T-type VG- Ca^{2+} channels → ↑ slow inward Ca^{2+} current - (3) Activation of electrogenic Na^+/Ca^{2+} antiport → driven by influx of Ca^{2+}
0	“Depolarisation” – Slow rate of depolarisation (Nb. smaller amplitude AP cf. “fast response” type)	Opening of L-type VG- Ca^{2+} channels → ↑ membrane Ca^{2+} permeability → ↑ Ca^{2+} influx
3	“Repolarisation” – Membrane potential returns to a “unstable” RMP	Late ↑ membrane K^+ permeability → ↑ K^+ efflux
Note – Phase 1 (“Spike”) and phase 2 (“Plateau”) do not exist		

Duration of AP: 150 msec

Conduction velocity: Slow (0.05 m/s) → means conduction is easily blocked and unidirectional block (re-entry) can occur

Important to note:

- These cells demonstrate “autorhythmicity” (I.e. property of heart that enables it to initiate its own heart beat) → this is due to the “pacemaker potential” (or “pre-potential”) characterised by a wandering RMP during phase 4 caused by cyclical changes in membrane ionic permeability that spontaneously depolarise the cell towards threshold
- The cyclical changes in membrane ionic permeability (I.e. ↓ K^+ , then ↑ Ca^{2+} , then ↑ K^+ permeabilities) are “intrinsic” to the cell → BUT external stimuli may modify it, and thus altering the speed of “pacemaker potential” (or phase 4):
 - o (i) PNS stimulation → hyperpolarises cell 2° to ↑ membrane K^+ permeability → slows “pacemaker potential”, thus ↓ spontaneously cardiac activity
 - o (ii) SNS stimulation → depolarises cell 2° to ↑ membrane Ca^{2+} permeability → speeds up “pacemaker potential”, thus ↑ spontaneous cardiac activity

Cells with the fastest “pacemaker potential” (or phase 4) become the pacemakers of the heart as they are the first to depolarise to threshold → usually the SA node

Aside – Cardiac muscle AP differs from a nerve AP as follows:

- (1) Cardiac muscle AP are longer in duration (250 msec or 150 msec vs 1 msec)
- (2) Cardiac muscle AP either have a “plateau phase” (fast response type) or “prepotential” (slow response type)

(B) Excitation-Contraction Coupling and Relaxation of Cardiac Muscle:

(I) Excitation-contraction coupling in cardiac muscle:

Occurs via “Calcium-induced calcium release” → amplification process where a small amount of Ca^{2+} enters the cell to cause temporary release of much larger amount of Ca^{2+} from the SR

Process:

- (i) AP arrives at cardiac muscle cell → spreads into interior of cell by T-tubules
- (ii) This opens up VG L-type Ca^{2+} channels (as part of “plateau” phase of cardiac muscle AP) → causes influx of extracellular Ca^{2+}

Note – Cardiac muscle does NOT contract if there is lack of Ca^{2+} in ECF!

- (iii) This triggers a substantial amount of Ca^{2+} release from the SR
- (iv) SR Ca^{2+} then binds Troponin → alters troponin-tropomyosin complex on actin → allows myosin (thick filament) and actin (thin filament) to interact, thereby causing muscle contraction

Important to note – The intracellular $[\text{Ca}^{2+}]$ in cardiac cell determines the force of contraction → normally, the amount of Ca^{2+} released during this process is insufficient to combine with all troponin and produce a submaximal contractile force → thus, factors that ↑ IC $[\text{Ca}^{2+}]$ will ↑ the force of contraction

(II) Relaxation in cardiac muscle:

Relaxation occurs as Ca^{2+} is pumped back by:

- (i) Ca^{2+} ATPase into the SR
- (ii) $3 \text{Na}^+ / 1 \text{Ca}^{2+}$ exchange – Needs Na^+ / K^+ ATPase ↓ IC $[\text{Na}^+]$ to facilitate extrusion of Ca^{2+}

Important to note – Catecholamines (NAd, Adr) act via cardiac β_1 -receptors to augment BOTH contraction and relaxation of cardiac muscle (Ie. speeds up BOTH emptying and filling of the heart) → these effects are Gs-mediated (Ie. stimulates AC → ↑ IC $[\text{cAMP}]$ → ↑ PKA activity):

- (i) Phosphorylates membrane-bound L-type VG- Ca^{2+} channels → opens them up and ↑ Ca^{2+} influx → ↑ IC $[\text{Ca}^{2+}]$ and ↑ contractile force
- (ii) Phosphorylates myosin → ↑ rate at which cross-bridge cycling occurs with actin → ↑ contractile force
- (iii) Phosphorylate phospholamban → ↑ active uptake of Ca^{2+} into SR → ↑ relaxation
- (iv) Phosphorylate troponin I → inhibit Ca^{2+} interaction with troponin C → ↑ relaxation

(C) Generation and Conduction of Cardiac Action Potentials:

Cardiac pacemaker cells (SA node, other atrial centres, AV node and Bundle of His) → generate inherent “automaticity” and “rhythmicity” of the heart

Note:

- Automaticity → property of heart that enables it to initiate its own heart beat
- Rhythmicity → degree of regularity in the repeated sequence of membrane repolarisation then spontaneous depolarisation of cardiac muscle that gives the heart a regular rhythm

SA node is the most active → contains cells with the fastest “pacemaker potential” (or phase 4), and thus become the “pacemakers” of the heart (I.e. set the HR) as they are the first to depolarise to threshold

Note – When the SA node is lost → the next most active group of pacemaker cells (I.e. next fastest “pacemaker potential”) then becomes the “pacemaker” of the heart and sets the HR → AV node or Bundle of His

Cardiac APs are conducted rapidly from these pacemaker cells through specialised tracts within the heart (“conducting system of the heart”) → provides rapid and coordinated cardiac contraction

Note:

- Cardiac AP travel from cell-to-cell through “Gap junctions” (which are cell membranes of adjacent cells fused together to form low resistance pathways) → allows electrical signals to easily cross from one cell to another
- These gap junctions are found alongside “Intercalated discs” (which act as a structural means to prevent adjoining cardiac cells from pulling apart during contraction)

“Conducting system of the heart” is as follows:

(1) SA node:

- Lies in RA close to entry of SVC
- Normal pacemaker of the heart (natural discharge rate = 100/min)
- Cardiac AP generated by SAN spreads directly through atrial muscle (by gap junctions b/t adjacent fibres) → causes simultaneous contraction of both atria



(2) Atrial conduction:

- Cardiac AP spreads from SAN node through atrial muscle (at rate of 1 m/s) → to (i) LA (via “Bachmann’s bundle”), and (ii) AV node (via anterior, middle and posterior internodal pathways)



(3) AV node:

- Lies at base of RA on right side of interatrial septum (near opening of coronary sinus)
- It has a natural discharge rate = 60-80/min

- AVN is the ONLY conducting pathway from atria to ventricles through the insulated fibrous atrioventricular ring → it has a slow conduction rate (0.05 m/s) and 0.1 sec delay in impulse transmission

Important to note – The significance of the slow conduction rate and delay in AVN conduction is:

- (i) It allows the atria to finish filling the ventricles before ventricular contraction begins
- (ii) It protects the ventricles from high rates of atrial depolarisation → AVN CANNOT transmit > 220 impulses/min (Nb. max atrial discharge rate = 400/min), meaning that the AVN fails to conduct all atrial impulses when the atrial discharge rate is high

- AVN conduction is affected by:
 - o (i) Vagal activity → hyperpolarises AVN by ↑ K^+ conductance → ↓ AVN transmission
 - o (ii) SNS activity → depolarises AVN by ↑ Ca^{2+} conductance → ↑ AVN transmission

(4) Bundle of His and bundle branches:

- Bundle of His runs down right side of interventricular septum → splits into RBB and LBB to each respective ventricle → LBB divides into anterior and posterior fascicles

(5) Purkinje fibres and ventricular cells:

- The bundle branches supply Purkinje fibres, which innervate ventricle cells
- Each Purkinje fibre and ventricular cells have large diameters → this means:
 - o (i) Very rapid conduction velocity (1-4 m/s) → causes rapid ventricular activation
 - o (ii) Long refractory period → blocks many premature atrial impulses that may have passed through AVN
- Although these cells are “fast response” type (Ie. lack unstable RMP), SOME demonstrate automaticity and rhythmicity (Ie. not obvious until CHB occurs) by spontaneously conversion to “slow response” type → they possess an intrinsic rhythm of 30-40/min

Process of ventricular activation:

- A wave of depolarisation travels down the Purkinje fibres in the interventricular septum from the AV node (spreading from left to right through the septum) down to the apex
- As a result:
 - o (i) Apical regions of ventricles are activated before the bases → this helps propel blood up and out of the ventricular chambers
 - o (ii) Endocardial surfaces are depolarised before epicardial surfaces
 - o (iii) RV is depolarised before LV (as RV wall is thinner than LV)

Note – Last part of ventricle to depolarise → epicardial surface of LV wall at base of heart (Ie. posterobasal LV)

(D) Properties of Cardiac Muscle:

Automaticity → property of heart that enables it to initiate its own heart beat

Important to note:

- This is a feature of “slow response” type cardiac cells (SA and AV nodal cells)
- The basis of “automaticity” is due to the “pacemaker potential” (or “pre-potential”) → characterised by a wandering RMP during phase 4 caused by cyclical changes in membrane ionic permeability that spontaneously depolarise the cell towards threshold
- The cyclical changes in membrane ionic permeability (I.e. $\downarrow K^+$, then $\uparrow Ca^{2+}$, then $\uparrow K^+$ permeabilities) are “intrinsic” to the cell → BUT external stimuli (Eg. PNS/SNS) may modify it, and thus altering the speed of “pacemaker potential” (or phase 4)

Cells with the fastest “pacemaker potential” (or phase 4) become the pacemakers of the heart as they are the first to depolarise to threshold → usually the SA node

Rhythmicity → degree of regularity in the repeated sequence of membrane repolarisation then spontaneous depolarisation of cardiac muscle that gives the heart a regular rhythm

Important to note:

- “Slow response” cells (AV and SN nodal cells) have an “unstable” or wandering RMP in phase 4 that spontaneously depolarise the cell towards threshold → possesses rhythmicity → form “pacemaker” of the heart
- “Fast response” cells (atrial, ventricular and Purkinje muscle cells) have a “stable” RMP in phase 4 → lacks rhythmicity → cannot be “pacemaker” of the heart (although ventricular and Purkinje cells can develop it in the setting of complete heart block!)

Conductivity → degree of propagation of depolarisation through the heart

Excitability → the magnitude of a stimulus required to depolarise a myocardial cell to threshold to generate an action potential (I.e. a cell that is more excitable is one that depolarises to threshold from a smaller stimulus)

Important to note – Excitability:

- (i) Relates to the slope of phase 0 (or upstroke) during myocardial cell depolarisation
- (ii) Is reduced (cf. to normal) during the “relative refractory period”, but progressively increases as phase 3 progresses (and full excitability restored when RMP reached at phase 4)
- (iii) Relates to the “conduction velocity” (I.e. steeper phase 0 slope = $\uparrow$ conduction velocity)

Irritability → indication in the context of a resting myocardial cell in phase 4 (I.e. RMP) of the:

- (i) Size of stimulus required to depolarise the cell (I.e. difference b/t RMP and threshold potential)
- (ii) Ease with which an arrhythmia may be induced

Important to note – ↑ irritability implies:

- (i) AP is easier to stimulate as the potential change to threshold is less (I.e. RMP and threshold potential difference is less) → cell membrane is easy to depolarise
- (ii) ↓ excitability (I.e. ↓ gradient of phase 0 (upstroke) and ↓ conduction velocity)
- (iii) ↑ likelihood of arrhythmias

Contractility → intrinsic ability of the myocardial fibre to shorten and thus increase the force of contraction that is independent of preload, afterload and heart rate

Important to note:

- IC $[Ca^{2+}]$ in cardiac cell determines the force of contraction:
 - o Normally, the amount of Ca^{2+} released during this process is insufficient to combine with all troponin and produces a submaximal contractile force
 - o Factors that ↑ IC $[Ca^{2+}]$ will ↑ the force of contraction → this occurs by:
 - (i) ↑ influx (via L-type Ca^{2+} channels) during the cardiac AP (during phase 2)
 - (ii) ↑ release of Ca^{2+} by the SR
 - (iii) Sensitizing troponin C to Ca^{2+}
- This property is unique to cardiac muscle only (I.e. not seen with skeletal muscle)

An aside:

Lusitrophy → degree of myocardial relaxation (I.e. GTN is a +ve lusiotroph)

Important to note:

- Myocardial relaxation is active (energy-consuming) process → involves active transport of Ca^{2+} (via Ca^{2+} ATPase) from cytoplasm to SR
- Myocardial relaxation causes diastolic relaxation → improves diastolic ventricular filling → ↑ preload and C.O.

Dromotrophy → speed of conduction through AV node (I.e. digoxin slows conduction → -ve dromotrope)

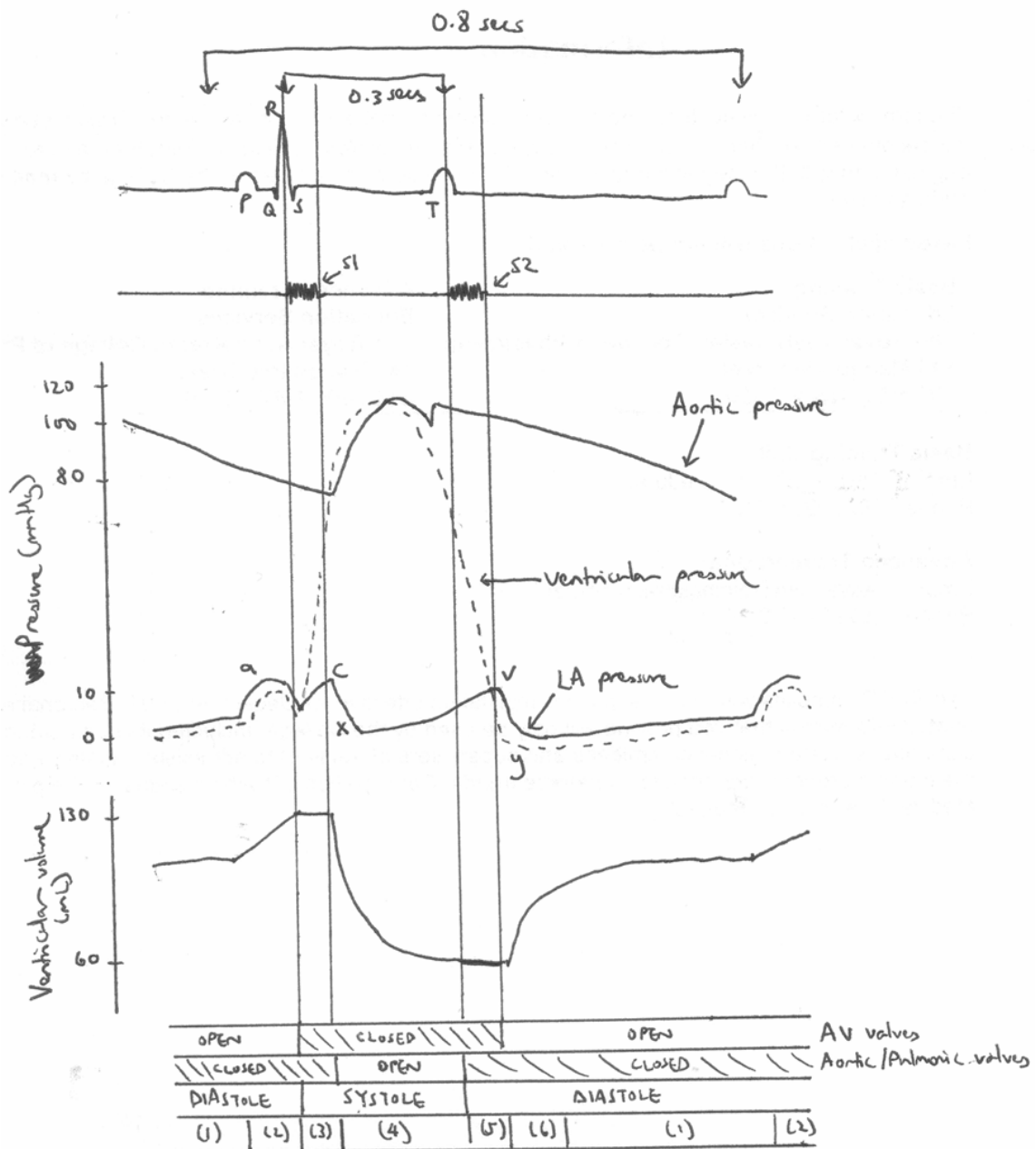
(E) Mechanical Events of the Cardiac Cycle:

Cardiac cycle has 2 phases defined by the mechanical activity of ventricular muscle:

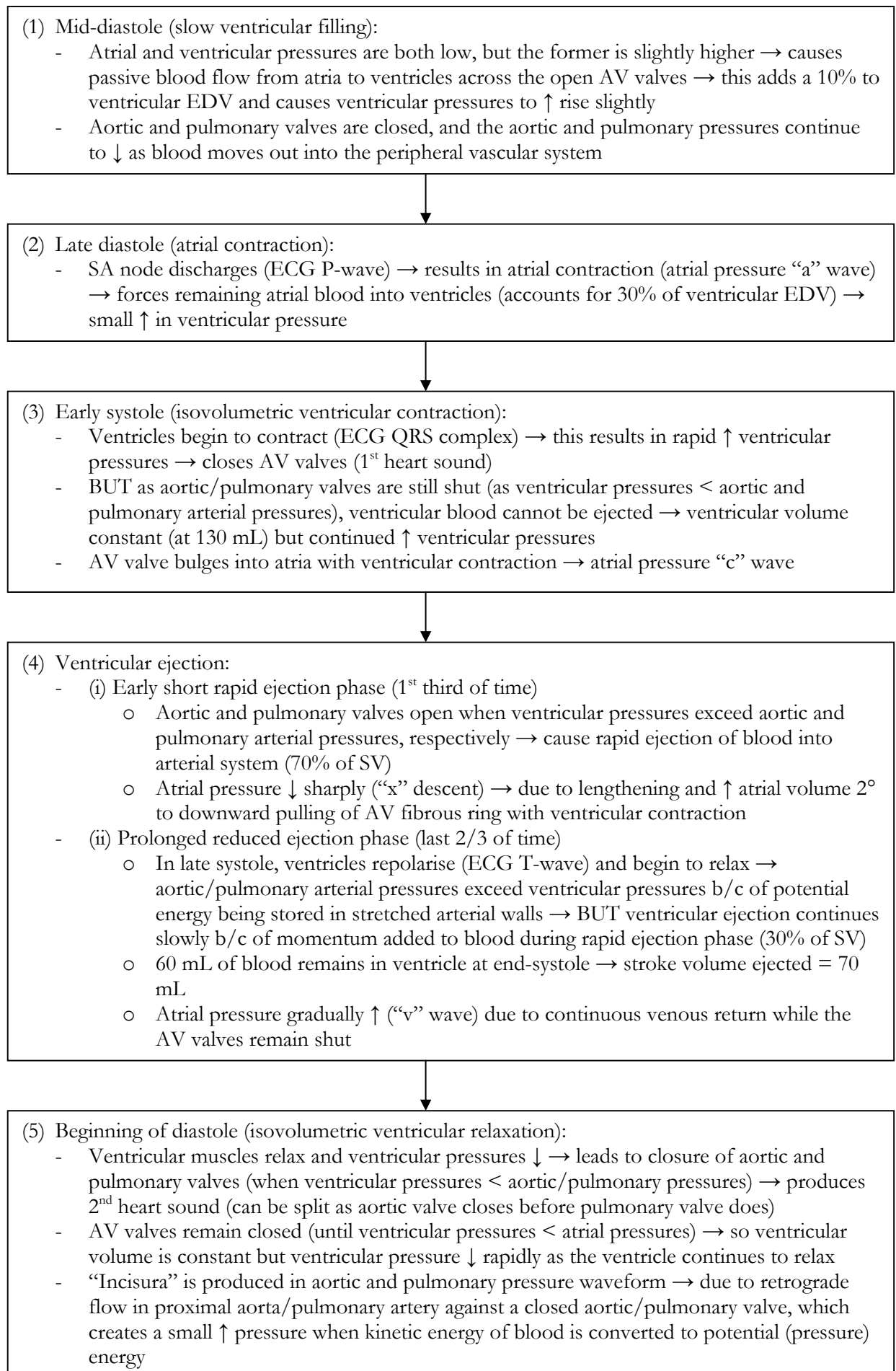
- (1) Systole (ventricular contraction) → divided into:
 - (i) Early systole (isovolumetric ventricular contraction)
 - (ii) Ventricular ejection (“Early short rapid ejection” and “Prolonged reduced ejection” phases)
- (2) Diastole (ventricular relaxation) → divided into:
 - (i) Beginning of diastole (isovolumetric ventricular relaxation)
 - (ii) Early diastole (rapid ventricular filling)
 - (iii) Mid-diastole (slow ventricular filling)
 - (iv) Late diastole (atrial contraction)

At a “resting” HR of 72 bpm → cardiac cycle lasts 0.8 secs (of which systole is 0.3 secs and diastole is 0.5 secs – whereby diastole is ~ 66% of cardiac cycle)

Important to note – At the “maximum” HR of 200 bpm → cardiac cycle is only 0.3 secs (of which systole and diastole are 0.15 secs each) → this results in compromise of ventricular filling during “early diastole”



The cardiac cycle proceeds in the following order:





(6) Early diastole (rapid ventricular filling):

- AV valves open when ventricular pressures ↓ below atrial pressures → leads to rapid passive ventricular filling with atrial blood (accounts for 60% of ventricular EDV)
- This causes rapid ↓ atrial pressures (“y” descent)

Important to note – Differences b/t left vs right heart:

- Cardiac cycle figure above retains a SIMILAR shape and proceeds as per the process described above
- Ventricular volumes remain the same (I.e. ventricular EDV = 130 mL; ventricular ESV = 60 mL; SV = 70 mL)
- Pressures of the atria, ventricles and arterial vessels differ:
 - LAP ↑ to 10 mmHg; RAP ↑ to 5 mmHg
 - Aortic (and LV) pressures ↑ from 80 mmHg diastolic to 120 mmHg systolic during ventricular ejection; pulmonary (and RV) pressures ↑ from 8 mmHg diastolic to 25 mmHg systolic during ventricular ejection

(F) Electrocardiograph (ECG) and Cardiac Electrical Activity:

Electrocardiogram (ECG) → the vector sum measurement of all electrical currents at the body surface that are generated by the electrical activity of the heart

Technique of ECG:

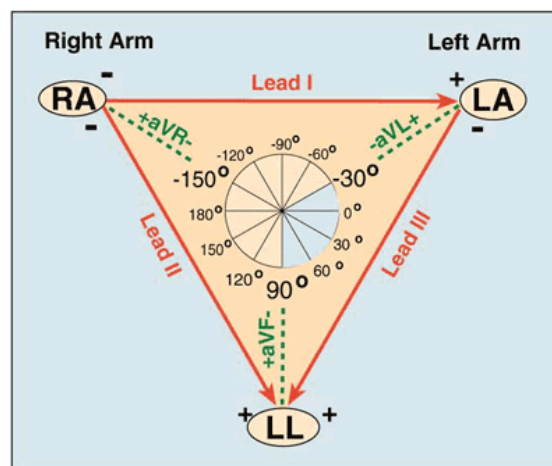
- Standard ECG involves placement of 12 electrodes on the body surface → detect small potentials (0.5-2 mV) at skin generated by spread of electrical activity of the heart through body tissues
- Electrodes made of Ag/AgCl → separated from skin by a foam pad soaked in a conducting gel
- ECG signals detected by these electrodes → send to electronic device that filters out noise and boosts the signal → then displayed on oscilloscope

12 lead ECG system:

- Standard limb leads (6x leads)
 - o Bipolar limb leads – Connecting one limb to another → 3x limbs are used (RA, LA, LL) with RL used as “earth” to minimise interference
 - Lead I: RA (-) to LA (+) at 0°
 - Lead II: RA (-) to LL (+) at 60°
 - Lead III: LA (-) to LL (+) at 120°
 - o Unipolar limb leads – Consists of unipolar leads from 3x limbs (RA, LA, LL)
 - aVR: RA (+) at -150°
 - aVL: LA (+) at -30°
 - aVF: LL (+) at 90°
- Chest leads (6x leads) → consists of unipolar leads on chest wall
 - o V1: R sternal margin at 4th ICS
 - o V2: L sternal margin at 4th ICS
 - o V3: Midway b/t V2 and V4
 - o V4: Intersection of 5th ICS and L MCL
 - o V5: Intersection of L MAL and horizontal line through V4
 - o V6: Intersection of L MAL with horizontal line through V4/V5

Principles of ECG:

- Based on “Einthoven’s Triangle” → electrical activity of the heart is at the centre of an equilateral triangle formed by the shoulders and pubic symphysis (with electrodes on both arms and the left foot approximating the corners of the triangle → standard 6x limb leads)

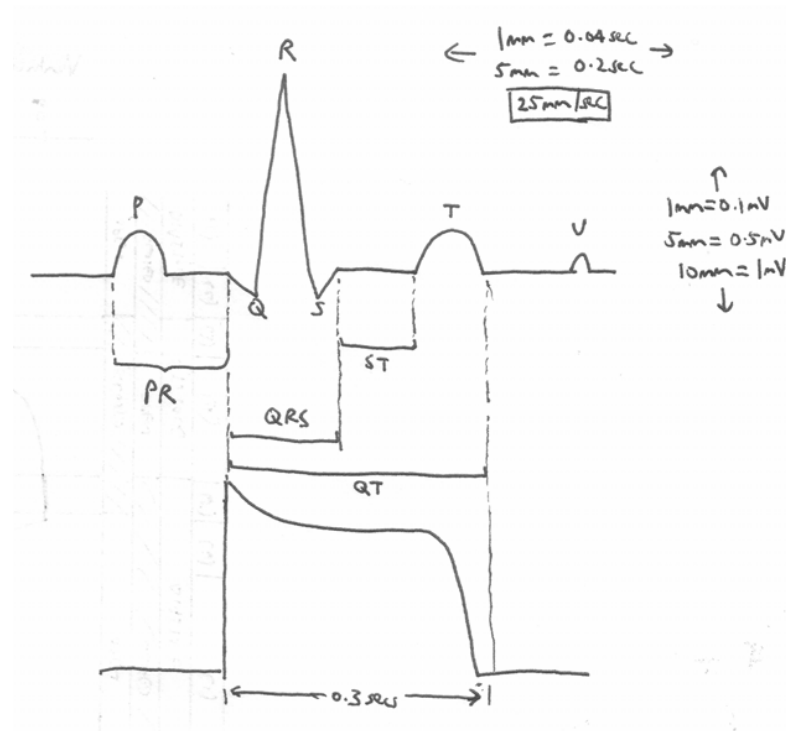


- “+ve deflection” in ECG occurs when wave of cardiac depolarisation travels TOWARDS electrodes, while “-ve deflection”

Important to note – ECG has characteristic waveform in lead II is b/c:

- (i) Atrial depolarisation commences in SAN and spreads down and to left to AVN → +ve deflecting P-wave
- (ii) Ventricular depolarisation starts in interventricular septum and spreads down and to right → -ve deflecting Q-wave
- (iii) Left ventricle depolarises first at the apex and epicardially → +ve deflecting R-wave
- (iv) Then remaining ventricles (RV, base and endocardium) → -ve deflecting S-wave
- (v) Ventricles repolarise from epicardium to endocardium → +ve deflecting T-wave

ECG waveform:



Calibration:

- Vertical calibration → 1 mV signal produces a vertical deflection of 10 mm (2x large square or 10x small squares) → 0.1 mV per mm (or small square)
- Horizontal calibration → paper speed is 25 mm/s → 0.04 s/mm (or small square)

Waves, intervals and segments:

- P-wave
 - Smooth and rounded deflection preceding QRS complex
 - Represents SA node and atrial depolarisation
- PR-interval
 - From start of P wave to start of QRS complex (usually Q-wave rather than R-wave) → 0.12-0.2 sec
 - Represents electrical conduction from SA node through atrial to AV node, then to ventricles via bundle of His → a good estimate of AV nodal function
- QRS-complex
 - Usually the largest deflection on ECG with “spiky” shape (starts from Q-wave to end of S-wave) → -ve deflection (Q-wave), followed by +ve deflection (R-wave), then another -ve deflection (S-wave) → < 0.12 msec with axis -30° to 90°
 - Represents ventricular depolarisation and spread of electrical activation through ventricular myocardium (Nb. atrial repolarisation also occurs here)

- ST-segment
 - From end of S-wave to beginning of T wave
 - Represents continued ventricular myocardial depolarisation
- T-wave
 - Broad and rounded wave following QRS complex
 - Represents ventricular repolarisation
- QT-interval
 - From beginning of Q-wave to end of T-wave
 - Corrected for HR as confounding factor → Corrected QTc = $QT/\sqrt{RR} = 0.36-0.44$ sec
 - Represents the duration of ventricular depolarisation
- U-wave
 - Broad and rounded wave following T-wave
 - Represents slow repolarisation of papillary muscles → caused by hypokalaemia, digoxin toxicity, bradycardia, ischaemia

Other features:

- “Sinus rhythm” → when every P-wave followed by QRS, every QRS preceded by P-wave, and P-wave upright in leads I-III
- Regularity → determined by PP-interval (atrial) and R-R interval (ventricular)
- Rate → 60-100 bpm

Use of ECG in anaesthesia:

- 3- or 5-lead ECG is used instead of standard 12-lead:
 - Lead II → best views of P and R waves → ideal for detecting arrhythmias and inferior wall ischaemia
 - CM5 (RA electrode on manubrium; LA electrode on V5, indifferent lead on left shoulder) → ideal for detecting ST segment changes due to LV ischaemia
 - CB5 (RA electrode over centre of right scapula and LA electrode over V5) → best view of P and QRS waves during cardiothoracic anaesthesia → ideal for detecting arrhythmias and ischaemia
- Two ECG modes exist:
 - (i) Monitoring mode:
 - Narrow frequency response range ~ 0.5-50 Hz → significantly reduces noise/interference but obscures ECG details (I.e. P and T-wave morphology and ST-segments)
 - High frequency limit of 50 Hz → ↓ artefact from muscle movement, electrical interference from equipment
 - Low frequency limit of 0.5 Hz → ↓ artefact from respiratory and body movement
 - (ii) Diagnostic mode:
 - Wider frequency response range ~ 0.05-100 Hz → allows monitoring of ST-segment and analysis of QRS, P and T-wave morphology, but introduces more noise/interference
 - High frequency limit of 100 Hz → allows QRS morphology and tachyarrhythmia assessment
 - Low frequency limit of 0.05 Hz → allows representation of P/T-wave morphology and ST segment analysis

Sources of error:

- ECG are easily affected by noise and interference as they measure very tiny electrical potentials at the skin (0.5-2 mV) → caused by:
 - (i) Electrical interference by any device using AC current (esp high-frequency diathermy) → minimise by ECG filters, shielding of leads/cables, differential amplifiers, Etc.

- (ii) Movement or shivering → minimised by placement over bony prominences and use of ECG filters
- (iii) High skin impedance → minimised by degreasing skin with EtOH and use of conducting gel with electrodes
- (iv) Incorrect electrode placement relative to heart

MEASUREMENT OF CVS FUNCTION

(a) *To outline the physics of blood flow.*

Blood is a type of fluid → has two types of flow patterns:

- (1) Laminar flow:

- Occurs when “viscous” forces (viscosity) predominate → $Re < 2000$:
 - (i) Tubes with small radius, absence of bends and smooth lining
 - (ii) Low fluid flow velocity (Ie. capillary and veins)
 - (iii) Fluid is highly viscous and/or low density (Ie. polycythaemia)
- Characterised by:
 - (i) Steady flow with no eddy currents or turbulence
 - (ii) Parabolic velocity profile → velocity greatest at centre of flow (2x the mean flow), and falls off rapidly to zero as wall approached
 - (iii) Resistance of flow obeys Hagen-Poiseuille’s equation:

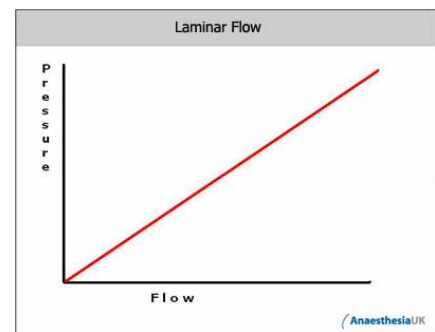
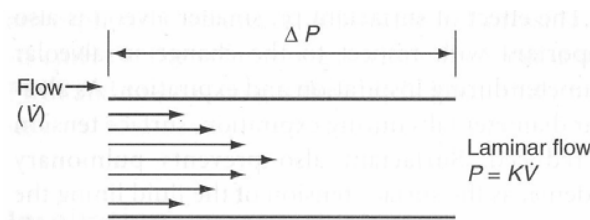
$$R = \frac{8nl}{\pi r^4}$$

n = viscosity
 l = length
 r = radius

- (iv) ↓↓↓ resistance to flow and driving pressure required (cf. turbulent flow)
- (v) Driving pressure is directly proportional to flow rate:

$$P = K \cdot V = R \cdot V$$

K = Constant
 P = Driving pressure
 V = Flow rate
 R = Airway resistance



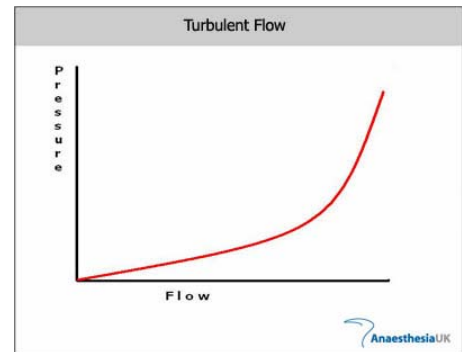
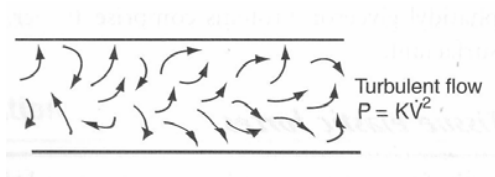
○ Thus, flow rate (V) is:

$$V = \frac{P}{R} = \frac{P \times (\pi r^4)}{8nl}$$

- (2) Turbulent flow:

- Occurs when “inertial” forces (density) predominate → $Re > 2000$:
 - (i) Tubes with large radius, sharp bends or rough lining (Ie. branch points, stenosed vessels and valves)
 - (ii) High fluid flow velocity (Ie. aorta)
 - (iii) Fluid with high density and/or low viscosity (Ie. anaemia)
- Characterised by:
 - (i) Flow occurs in disorganised stream lines and eddy currents are present
 - (ii) Absence of velocity profile
 - (iii) Resistance of flow does NOT obey Hagen-Poiseuille’s equation
 - (iv) ↑↑↑ resistance to flow and driving pressure required (cf. laminar flow)
 - (v) Driving pressure is proportional to the square of flow rate

$$P = K \cdot V^2 = R \cdot V^2$$



- Thus, flow rate (V) is:
$$V = \frac{k \cdot r^2 \cdot \sqrt{P}}{\eta \cdot L}$$

Nature of blood flow:

- Determined by “Reynolds number” (Re) → dimensionless ratio of inertial to viscous forces of fluid:

$$Re = \frac{2rvd}{\eta}$$

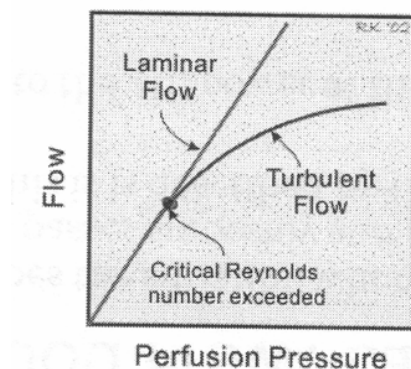
r = radius
 v = velocity of gas flow
 d = density of gas
 η = viscosity of gas

- Turbulent flow is likely if $Re > 2000$; Laminar flow is likely if $Re < 2000$

Nb. “Critical velocity” → velocity of fluid where $Re = 2000$ (I.e. transition of laminar to turbulent flow) for a given set of conditions

Significance of nature of blood flow:

- Laminar flow → blood flow is proportional to perfusion pressure
- Turbulent flow → blood flow is proportional to the square-root of perfusion pressure (so at a given perfusion pressure, blood flow is ↓↓↓)



Important to note – Viscosity of blood → reduced with → (i) ↑ blood flow, (ii) ↓ Hcrit, (iii) ↓ vessel diameter

(b) **To give a detailed account of the various methods of measuring blood pressure.**

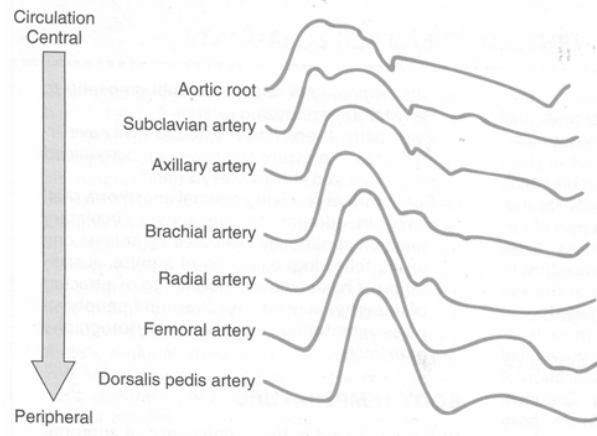
(I) Overview of blood pressure measurement:

Definition of blood pressure:

- “Blood pressure” is the pulsatile pressure in the arterial system caused by ejection of blood into the vascular system by rhythmic left ventricular contraction
- Types of BP measured:
 - (i) Systolic BP → peak pressure generated during systolic contraction
 - (ii) Diastolic BP → trough pressure generated during diastolic relaxation
 - (iii) Pulse pressure → difference b/t SBP and DBP
 - (iv) Mean arterial pressure → time-weighted average of arterial pressure during pulse cycle → where $MAP = DBP + 1/3 (SBP - DBP)$

Variations in blood pressure:

- Arterial BP varies within the arterial tree → as the pulse moves more peripherally:
 - Arterial BP waveform becomes narrower and increases in amplitude → exaggerates SBP and pulse pressure → due to changes in vessel diameter, vessel elasticity, reflection of wave pattern from vessel walls
 - Loss of dicrotic notch (which is present due to intra-aortic vibrations)



- Arterial BP varies with respect to level of measurement site relative to the heart → due to gravity-dependent effect on BP (I.e. falsely ↑ BP if manometer below level of heart)

Basis for measuring blood pressure:

- Adequate O_2 delivery to tissues needs to be maintained → BUT it is impractical to measure organ-specific perfusion and oxygenation during anaesthesia
- As a result → arterial BP is measured instead as it is directly related to flow:

$$\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$$

- Note – Arterial BP is an indicator of tissue perfusion (rather than a direct measure) → b/c vascular resistance is not known (I.e. if R is ↑, then flow remains ↓ despite a ↑ BP)

(II) Non-invasive blood pressure (NIBP) measurement:

All NIBP measurement (except arterial tonometry) involves an inflatable cuff connected to a manometer:

Inflatable cuff:

- Properly positioned on extremity being measured (usually arm) → with centre of bladder over artery (usually brachial artery)
- Cuff width should be 20-50% greater than diameter of extremity → as a narrow cuff will overestimate BP (as it needs more pressure to occlude an artery), and a wide cuff will underestimate BP (as it needs less pressure to occlude an artery)
- Cuff, tubing and connections should be free of leak

Manometer:

- Hg-type → must read zero before use and kept vertical during measurement
- Aneroid gauge → more portable and less toxic, but requires more frequent calibration
- Electronic (pressure transducer)

Methods of NIBP measurement:**(1) Palpation**

BP measured	SBP only
Principle	Blood flow is restored in a peripheral artery when a BP cuff is deflated below SBP → produces a palpable pulse that correlates with SBP
Method	- Palpable peripheral pulse is located first → then BP cuff is placed proximal to it and inflated to a pressure above the expected systolic BP → causes occlusion of blood flow and loss of pulse - ↓ cuff pressure by 2-3 mmHg per second until pulse palpable again → pressure when this happens is measured as the SBP
Advantages	Simple and inexpensive
Disadvantages	- (i) Tend to underestimate SBP (due to insensitivity of touch and delay in flow under cuff and distal pulsation) - (ii) Does not measure MAP or DBP - (iii) Issues with cuff (positioning, size, leak) and manometer (calibration, positioning)

(2) Doppler probe

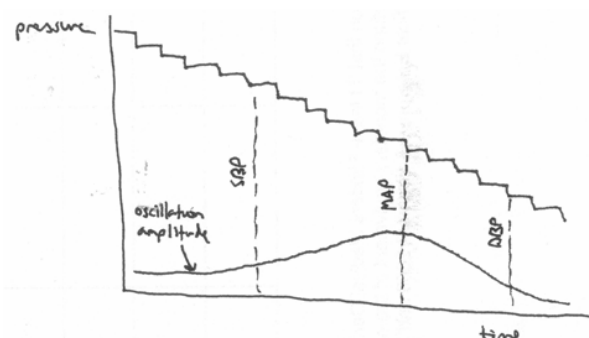
BP measured	SBP and DBP
Principle and method	- Doppler effect → shift in frequency of sound waves when source moves relative to observer - Restoration of blood flow in a peripheral artery when BP cuff is deflated below SBP is detected by Doppler frequency shift of RBC flowing in artery → measures SBP - Lateral arterial wall movement due to intermittent opening/closing of vessel walls between SBP and DBP → measures SBP and DBP
Advantages	Greater sensitivity than palpation technique (esp in obese, paediatric and shocked patients)
Disadvantages	- (i) Probe needs to be kept directly over artery - (ii) Interference due to movement artefact and diathermy - (iii) Need to apply gel between skin and probe - (iv) Issues with cuff (positioning, size, leak)

(3) Auscultation

BP measured	SBP and DBP (SBP is more accurate)
Principle	Turbulent flow is produced when a peripheral artery is partly collapse when a BP cuff is inflated to a pressure between SBP and DBP → audible by stethoscope
Method	- Palpable peripheral pulse is located first → then BP cuff is placed proximal to it and inflated to a pressure above the expected systolic BP - ↓ cuff pressure by 2-3 mmHg per second until Korotkoff sounds (indicating turbulent flow) are audible by stethoscope: - o 1st Korotkoff phase (snapping tone) → indicates SBP - o 2nd Korotkoff phase (murmurs)

	○ 3rd Korotkoff phase (thumping) ○ 4th Korotkoff phase (muffling) ○ 5th Korotkoff phase (loss of all sound) → indicates DBP
Advantages	Simple and inexpensive
Disadvantages	- (i) Hypotension, movement, marked peripheral vasoconstriction → difficult to auscultate Korotkoff sounds - (ii) Auscultatory gap (esp in HTN patients) → Korotkoff sounds cannot be heard → leads to inaccurate DBP readings - (iii) Issues with cuff (positioning, size, leak) and manometer (calibration, positioning)

(4) Oscillometry

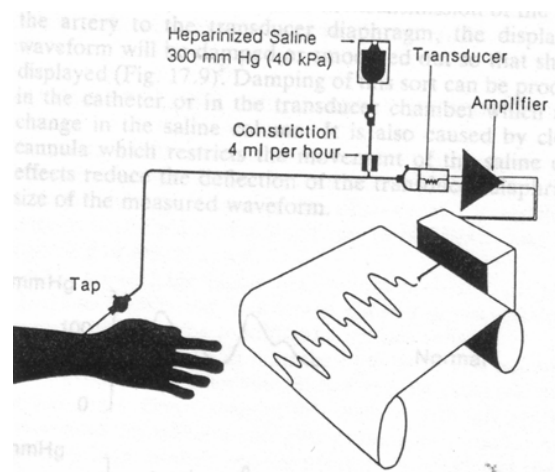
BP measured	MAP (most accurate) > SBP >> DBP (least accurate → some machines calculate it from measured MAP and SBP)
Principle	Based on oscillometry → arterial pulsations cause oscillations in cuff pressure which is then measured by a pressure transducer within the cuff: - Point of maximal pressure oscillation amplitude → MAP - Point of significant rise in amplitude of pressure oscillation → SBP - Point of significant fall in amplitude of pressure oscillation → DBP - Frequency of pressure oscillation → HR
Method	- Palpable peripheral pulse is located first → then BP cuff is placed proximal to it and inflated using air pump to a pressure above the expected systolic BP - Cuff pressure is then ↓ by 2-3 mmHg per second via a bleed valve and held briefly → pressure transducer within cuff measures the oscillations in cuff pressure caused by arterial pulsations → oscillations above a baseline level are recorded → this process is repeated multiple times until cuff is fully deflated - Characteristic pattern of cuff pressure oscillation is demonstrated: ○ Above SBP and below DBP → small oscillations in pressure ○ At SBP → significant rise in amplitude of pressure oscillation ○ At MAP → maximal amplitude of pressure oscillation reached ○ At DBP → significant fall in amplitude of pressure oscillation - HR → determined by frequency of oscillations  - Subsequent NIBP measurement → cuff pressure is inflated to 25 mmHg above last SBP measurement
Advantages	- (i) Simple and inexpensive - (ii) Portable and versatile - (iii) Fast response time and accurate
Disadvantages	- (i) DBP is derived → inaccurate - (ii) Movement artefact - (iii) Arrhythmias (esp AF) → inaccurate results as BP varies with each ventricular contraction → machines need identical consecutive pulse waves for measurement confirmation - (iv) Hypotension (esp SBP < 50 mmHg) → inaccurate results - (v) Cannot do frequency readings (max 1x/min) → if used consistently, can impede blood flow in extremity! - (vi) Cannot be used during cardiopulmonary bypass - (vii) Issues with cuff (positioning, size, leak)

(5) Arterial tonometry

BP measured	Continuous pulse recording → tracing similar to IABP waveform
Principle	Measures beat-to-beat BP by sensing pressure required to partially flatten a superficial artery supported by bony structure (Eg. radial artery)
Method	Consists of several independent pressure transducers applied to skin over artery → contact stress b/t transducer over artery and skin reflects intraluminal pressure
Advantages	Continuous pulse recording (like IABP)
Disadvantages	Need for frequent calibration, and inaccuracies due to movement artefact

(III) Invasive blood pressure measurement:

Components of invasive arterial BP:



- (1) Intra-arterial cannula
 - Short and narrow cannula is inserted into a peripheral artery (usually radial artery) → connected to a fluid-filled tubing system
- (2) Fluid-filling tubing
 - Acts as a column of non-compressible, bubble-free fluid between arterial blood from cannula and the pressure transducer → permits “hydraulic coupling”
- (3) Infusion system
 - Pressured bag (300 mmHg/40 kPa) of heparinised saline is attached to the fluid-filling tubing via a “flush system” → provides a continuous slow infusion at < 4 mL/hr to maintain cannula patency and prevent clotting
 - “Fast fluid flush” can be performed → (i) assess natural frequency and damping of system, and (ii) keep the tubing system clear
- (4) Pressure transducer
 - Movement of pressure transducer’s diaphragm caused by arterial pressure changes in tubing fluid is converted into an electrical signal by either stretching or compressing “strain gauges” within a “Wheatstone bridge circuit”
- (5) Microprocessor
 - Electrical signal from the transducer is processed, amplified and displayed as a pressure waveform over time on a screen

Principles of invasive arterial BP:

- Pressure waveform of arterial pulse at cannulated artery is transmitted to a column of fluid within the tubing system, which then transmits it to a pressure transducer (via “Hydraulic coupling”) → converted into electrical signal using strain gauges within a Wheatstone bridge → sent to microprocessor
- Since arterial waveform consists of many sine waves of varying amplitudes, frequency, wavelength, and phases → microprocessor uses “Fourier analysis” to break down the

arterial pressure waveform into component sine waves → then reconstructs it from a fundamental wave and at least 8-10 harmonic waves of higher frequency

For example → with a HR of 60-180/min, fundamental frequency (F_0) of fundamental wave is b/t 1-3 Hz → to reconstruct an arterial waveform, harmonic frequencies of 8-10 Hz (at HR 60/min) up to 24-30 Hz (at HR 180/min) are required

Accuracy of invasive arterial BP measurement:

(1) “Static accuracy” → easily achieved by calibrating the catheter-transducer system via:

- (a) Zeroing
 - $P_{\text{ATMOSPHERIC}}$ must be excluded from arterial pressure measurement → done by exposing transducer to $P_{\text{ATMOSPHERIC}}$ and calibrating this pressure reading to zero
- (b) Levelling
 - Transducer must be set at an appropriate level to the patient (I.e. level of the heart), otherwise error due to $P_{\text{HYDROSTATIC}}$ exerted by a column of fluid above (or below) the transducer being measured is added to the arterial BP measurement

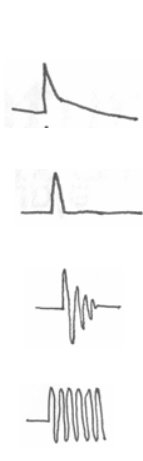
Note → 10 cm deviation of the transducer = 7.4 mmHg error:

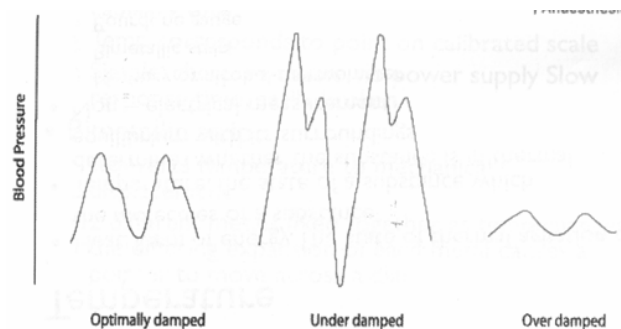
- Transducer too low → arterial BP falsely elevated (as it includes $P_{\text{HYDROSTATIC}}$ of fluid column above the transducer)
- Transducer too high → arterial BP falsely depressed (as pressure measured is less $P_{\text{HYDROSTATIC}}$ of the fluid column below the transducer)

(2) “Dynamic accuracy” → more difficult to achieve as the catheter-transducer system is influenced by certain mechanical parameters (Eg. elasticity, mass, friction of system)

- (a) Resonant (natural) frequency of the system
 - Defined as the frequency at which the system oscillates freely
 - Most IABP systems have a high resonant frequency of 100-200 Hz to avoid signal amplification and distortion → this is because:
 - If the resonant frequency of the system lies close to the frequency of any sine wave component of the arterial waveform → system will resonate (I.e. system's oscillation will superimpose on oscillation of arterial waveform) → cause excessive signal amplification and distortion characterised by falsely ↑ SBP, ↓ DBP and widened pulse pressure
 - To avoid this, resonant frequency of system must be at greater than the 8th to 10th harmonic frequency of the fundamental frequency → thus, to keep the system accurate for HR up to 180/min ($F_0 = 3$ Hz), resonant frequency of system must be > 24-30 Hz
 - The system's resonant frequency can be increased by:
 - (i) ↓ its length (I.e. shorter cannula and tubes, avoiding 3-way taps)
 - (ii) ↓ its compliance (I.e. stiffer tubes)
 - (iii) ↓ the density of the fluid within the system
 - (iv) ↑ the diameter of the tubing and cannula
 - System's resonant frequency is assessed by “Fast flush” test (I.e. system flushed with high-pressure saline) → generates undershoot and overshoot of waves that resonate at the system's resonant frequency → this frequency is calculated by dividing the screen speed by the wavelength of the wave produced
- (ii) Damping of the system
 - Defined as the tendency of an oscillating system to lose its energy → attenuates the amplitude of oscillations towards baseline as a result of viscous and frictional forces within the system
 - Levels of damping:
 - (i) Overdamping (DC > 1.0) – System does not oscillate freely, does not overshoot its resting point, lacks high frequency oscillations, and is very



- 
- slow to respond → causes falsely ↓ SBP, falsely ↑ DBP and loss of fine details of waveform (Eg. dichrotic notch)
 - (ii) “Critical damping” ($DC = 1$) – Minimal amount of damping needed to prevent any overshoot of oscillation; system slow to respond
 - (iii) “Optimal damping” ($DC = 0.64$) – Provides a compromise between the speed of the system with its accuracy (minimises overshoot of oscillations, phase and amplitude distortion, and provides maximal frequency response)
 - (iv) Underdamping ($DC < 0.7$) – System oscillates freely, overshoots its resting point, has very high frequency oscillations, and is quick to respond → causes falsely ↑ SBP and falsely ↓ DBP
 - (v) Lack of damping ($DC = 0$) – System oscillates at its resonant frequency with no decrement in oscillation over time



- The system’s damping is often caused by:
 - (i) Addition of 3-way taps
 - (ii) Bubbles and clots within the system
 - (iii) Arterial vasospasm
 - (iv) Kinking of the tubing or cannula
 - (v) Narrow, long or compliant tubing system
- “Damping coefficient (DC)” is measured by “Fast flush test” → amplitude ratio of 2 consecutive resonant waves (smaller wave to larger one)

Important to note:

- “Static calibration” → determines accurate measure of MAP only (physiologically important as it determines perfusion pressure of tissues)
- “Dynamic calibration” → determines accurate measure of SBP, DBP and pulse pressure only (less physiologically important)

Advantages and disadvantages of invasive arterial BP:

- Advantages:
 - (i) Gold standard of arterial BP measurement – High accuracy (esp with low BP, such as shock) and high reliability (esp with fluctuating CO, such as AF)
 - (ii) Continuous beat-to-beat BP measurement is useful for close monitoring of patients with labile BP (Eg. shock, MI)
 - (iii) Useful where NIBP is not practical (Eg. burns, obesity, reduce risk of tissue injury with frequent NIBP in prolonged cases)
 - (iv) Permits arterial blood sampling
 - (v) Waveforms can be analysed to provide info regarding CV status (“pulse contour analysis”)
- Disadvantages:
 - (i) Risk of arterial damage (including thrombosis and haematoma)
 - (ii) More costly to manage
 - (iii) Requires technical skill to set up

(c) *To explain the various methods of measuring cardiac output as well as their limitations.*

Cardiac output (C.O.):

- C.O. → volume of blood pumped by the heart per minute (~ 5 L/min in 70 kg male)

$$\text{C.O.} = \text{HR} \times \text{SV}$$

- It is a measure of the fundamental ability of the heart to deliver blood to/from the tissues

Methods of measuring C.O.:

(1) Fick Method:

- Based upon “Fick’s Principle” – Expression of the law of conservation of mass → whereby the amount of substance taken up (or excreted) by an organ per unit time is equal to the arterio-venous difference of the substance times the blood flow

$$\text{Amount of substance} = ([]_{\text{ARTERIAL}} - []_{\text{VENOUS}}) \times (\text{blood flow})$$

$$\text{So} \rightarrow \text{Blood flow} = \frac{\text{Amount of substance}}{([]_{\text{ARTERIAL}} - []_{\text{VENOUS}})}$$

- Two techniques:

- o (i) Direct Fick method:

- Uses uptake of O₂ by lungs and arterio-venous [O₂] gradient to calculate pulmonary blood flow → PBF is the same as C.O.

$$\text{PBF} = \text{C.O.} = \frac{\text{VO}_2}{(\text{CaO}_2 - \text{CvO}_2)} = \frac{250 \text{ mL/min}}{(200 \text{ mL/L} - 150 \text{ mL/L})} = 5 \text{ L/min}$$

- Technique – VO₂ = slope of tracing obtained from patient rebreathing O₂ from Benedict-Roth spirometer through soda-lime absorber; CaO₂ obtained from arterial blood (arterial line); CvO₂ from MVB (PA catheter)

Note: This is the most accurate method for C.O. measurement → BUT it is invasive, requires time for sample analysis, and accurate O₂ consumption samples are difficult to acquire

- o (ii) Indirect Fick method:

- C.O. is determined by measuring content of one of blood gases (usually CO₂) → uses elimination of CO₂ by lungs and arterio-venous [CO₂] gradient to determine PBF and C.O.

$$\text{C.O.} = \frac{\text{Rate of CO}_2 \text{ elimination from lung}}{(\text{CvCO}_2 - \text{CaCO}_2)} = \frac{200 \text{ mL/min}}{52 \text{ mL/L} - 48 \text{ mL/L}} = 5 \text{ L/min}$$

- Technique – Rate of CO₂ elimination from lung = (expiratory flow rate) x (% CO₂ in expired air); CvCO₂ obtained from MVB (PA catheter); CaCO₂ from arterial blood (arterial line)

(2) Indicator-dilution technique:

- Injected exogenous substance (indicator) is used → ideal features of indicator include:

- o (i) Non-toxic
- o (ii) Rapidly mix with blood
- o (iii) Not lost within circulation
- o (iv) [Indicator] must not be influenced by [Hb]
- o (v) Does not affect C.O.
- o (vi) Easily and accurately measured with a measurement technique

- Principle:

- If a known quantity of an indicator substance is introduced to an unknown flow, the flow will be equal to the amount of indicator injected divided by the average downstream concentration of the indicator

$$\text{Flow} = \frac{\text{Volume}}{\text{Time}} = \frac{\text{Indicator dose}}{\text{Average downstream [indicator]}}$$

- “Average downstream [indicator]” obtained by measuring the downstream [indicator] over time → then integrating the area under the measured concentration-time curve

$$Q = \frac{q}{c \cdot dt}$$

Q = blood flow

q = quantity of indicator injected

c = indicator concentration

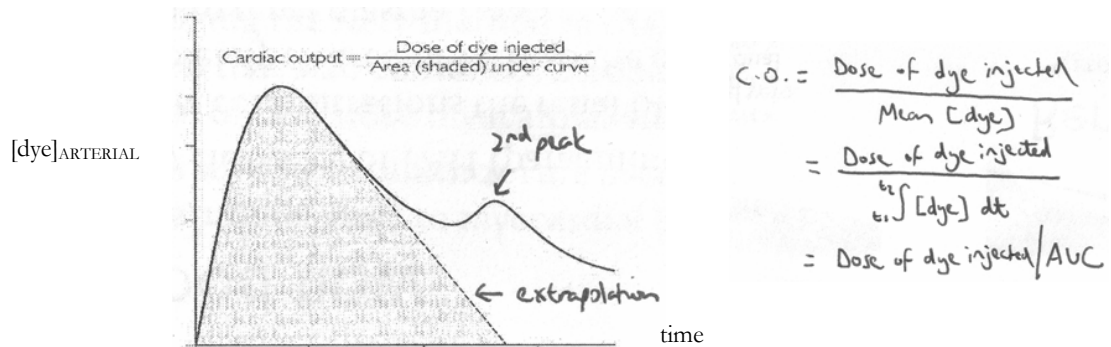
dt = change in time (between t1 and t2)

Note – This equation is highly simplified → full version is the “Stewart-Hamilton” equation → uses other variables (indicator used, volume and speed of injection)

- Two techniques exist:

- (i) Dye-dilution technique

- Known amount of indicator dye (indocyanine green or lithium) injected into RA (via RA catheter) → then arterial blood is continuously sampled (via arterial line) → [dye] in arterial blood is measured using spectrophotometry
- Plot of [dye]_{ARTERIAL} vs. time generated (Nb. recirculation of dye occurs before the last portion of the initial circulation is measured → 2nd peak)



- Total [dye]_{ARTERIAL} during 1x C.O. cycle determined by the AUC (Nb. requires extrapolation of curve to eliminate effect of dye recirculation)

Issues:

- (i) PA/RA catheter insertion is invasive and carries complications (Eg. PTX, haemorrhage)
- (ii) Problems with dye use (allergic reactions, recirculation of dye (and need to extrapolate data from graph), and background tracer build-up)
- (iii) Need for arterial puncture for sampling

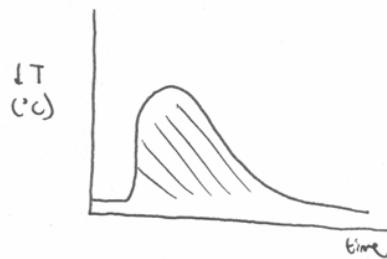
- (ii) Thermal dilution:

- PA catheter with 2 channels inserted into IJV → 1st channel in SVC/RA (injecting channel) and 2nd channel in PA (thermistor)
- Thermal mass (cold solution of known volume of either saline or D5W) injected into RA through 1st channel of PA catheter → mixes with warm blood within RA → temperature in PA measured by thermistor in 2nd channel of PA catheter

Aside:

- Use of D5W → ↓ risk of ↑ Na⁺ load with repeated injections, such as hypernatraemia and ↑ ECFV (cf. saline)
- Use of saline → ↑ accuracy due to ↑ temperature Δ (cf. D5W)

- Temperature change b/t RA and PA determined → produce Δ temperature vs time curve → software then integrates this curve to determine the “average downstream [thermal mass]” (based on measured temperature, and known density, volume and specific heat of injectate)
- C.O. then calculated by dividing the “average downstream [thermal mass]” from the “injected thermal mass” (also based on temperature, density, volume and specific heat of the injectate)



$$C.O. = \frac{\text{Amt. of injected thermal mass}}{\text{Avg. downstream [injected thermal mass]}}$$

Nb. C.O. is indirectly proportional to (i) Δ temperature b/t the 2 channels and (ii) AUC of temperature-time curve

Advantages:

- (i) Thermal mass → less recirculation, easier dispersion, non-toxic, smaller volumes used, and can be repeated rapidly (cf. dye)
- (ii) No need for arterial puncture (cf. dye)

Issues:

- (i) Accuracy +/- 10-25%
 - Maximised by doing repeated measurements (5 readings taken with middle 3 averaged) and discarding any obviously spurious measurements, smooth and rapid injection, using precisely known injectate volume and temperature, and injecting at the same phase of the respiratory cycle
 - Inaccuracies may be introduced by patient factors (R-L shunts, tricuspid regurgitation, high positive ventilatory pressures), calibration factors (several variables, such as specific gravity and specific heat of injectate and blood, are required), equipment factors (Eg. misplaced catheter, improper injection technique)
- (ii) Arrhythmias (due to rapid injection of cold thermal mass)
- (iii) PA catheter insertion is invasive and carries risks of complications (Eg. PTX, haemorrhage)

(3) Transoesophageal doppler U/S:

- Technique – Doppler U/S placed into oesophagus → C.O. determined by measuring cross-sectional area (CSA) and mean blood flow velocity of descending aorta
- Principle – C.O. is calculated using the following determined variables:

$$C.O. = HR \times SV \longrightarrow \text{where } SV = v \cdot ET \cdot CSA$$

v = mean aortic blood flow velocity (cm/sec)
 ET = systolic ejection time (sec)
 CSA = aortic cross-sectional area (cm²)

- (i) Mean blood flow velocity of descending aorta → determined by measuring the Doppler frequency shift of a transmitted U/S beam against moving RBC within descending aorta blood flow

$$F_d = \frac{2F_t V \cos\theta}{C}$$

F_d = frequency shift

F_t = transmitted frequency

V = velocity of flow

$\cos\theta$ = cosine of the angle of transmitted frequency to flow

C = velocity of sound through medium (approx 1560 m/s)

Note – When calculating velocity of blood flow:

- Transmitted U/S frequency is known → frequency shift is measured
- Cosine of angle of transmitted frequency to flow is assumed to be 1 → b/c U/S beam should be oriented in direction that is parallel to blood flow → so angle is small (usually < 20°)
- Velocity of sound through tissue → assumed to be ~ 1560 m/s

- (ii) Systolic ejection time and aortic CSA → determined by U/S
- (iii) HR → easily measured
- Issues:
 - (i) Nature of blood flow is pulsatile (and NOT fixed) → but only mean blood flow is measured (as mean blood flow velocity is measured)
 - (ii) ↓ accuracy when probe directed along artery is not parallel to flow – If $\theta > 60^\circ$ → ↓ accuracy of calculated velocity; $\theta = 90^\circ$ → no Doppler shift
 - (iii) Only descending aorta flow is measured (excluding coronary, cerebral, upper limbs) → total C.O. needs to be corrected (as descending flow ~ 80% C.O.)
 - (iv) Less accurate than thermodilution technique → but less invasive and continuous

(4) Imaging techniques:

- (a) Ventriculography (radiographic and radionuclide)
 - Contrast injected into LV and X-ray images are recorded → Δ LV diameter used to estimate Δ LV volume → used to estimate LVEDV and LVEF
- (b) Echocardiography (transthoracic or transoesophageal)
 - B or M mode used to estimate several parameters → assess C.O., LV filling (EDV and ESV), EF, wall motion abnormalities and contractility

(5) Electromagnetic flowmeter:

- Technique – Artery is placed into a magnetic field perpendicular to direction of blood flow → induced electrical field is perpendicular to both blood flow and magnetic field → measured by 2 electrodes touching opposite sides of artery
- Principle – Applies “Faraday’s Law” of electromagnetic induction – If a conductor (such as blood) moves through a magnetic field, an electrical field is induced → the magnitude of this field (E) is perpendicular to and proportional to the applied magnetic force (B) and the flow velocity of the conductor (v)

$$E = v.B.\sin\theta \text{ (where } \theta = \text{angle b/t B and v)}$$

- Issues:
 - (i) Measures mean blood flow velocity across arterial diameter → averages out the velocity profile of arterial blood flow
 - (ii) Machine is large, cumbersome and generates lots of heat → used experimentally only

(6) Arterial pressure waveform analysis (E.g. PiCCO):

- Characteristic impedance approach (Wesseling method) → pulse contour analysis for estimating SV
- Principle:
 - Based on $CO = MAP/SVR$
 - Pressure used for calculation is derived from arterial waveform (systolic portion from end-diastole to end of ejection phase), which is divided by characteristic impedance (~ resistance). Uses correction factors also
- Advantages; Safer, cheaper, continuous, easier to use, and accurate

(7) Others:

- Impedance plethysmography
- Ballistocardiography
- Sonomicrometry

(d) *To outline methods and principles used to measure regional blood flow.*

Cerebral blood flow (CBF) measurement:

- CBF is 750 mL/min
- Principle – Based on “Fick’s principle” (see above) → uses uptake of N₂O by brain and arterio-venous [N₂O] gradient to calculate CBF
- Technique – Kety-Schmidt method:
 - o Based on known solubility of N₂O in brain tissue and measurement of N₂O in arterial blood (sampled from arterial line) and cerebral venous blood (sampled IJV CVC) during 10 minute breathing of a 15% N₂O-containing mixture
 - o Arterial and venous samples are taken every 1 minute

$$\text{Cerebral blood flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

$$\text{Clearance} = \frac{\text{N}_2\text{O uptake rate}}{\text{Arterial [N}_2\text{O]}}$$

$$\text{Extraction ratio} = \frac{(\text{Arterial [N}_2\text{O]} - \text{Cerebral venous [N}_2\text{O]})}{\text{Cerebral venous [N}_2\text{O]}}$$

Coronary blood flow (CoBF) measurement:

- CoBF is 250 mL/min
- Principle – Based on “Fick’s principle” (see above) → uses uptake of N₂O by myocardium and arterio-venous [N₂O] gradient to calculate CBF
- Technique:
 - o (i) Kety-Schmidt technique – Similar to that used to measure CBF, except catheter is inserted into coronary sinus. Assumes coronary venous blood is typical of entire myocardial effluent
 - o (ii) Radionuclide method (Thallium-201) → distribution proportional to myocardial blood flow

Pulmonary blood flow (PBF) measurement:

- PBF is 5 L/min
- Principle – Based on “Fick’s principle” (see above) → uses uptake of O₂ by lungs and arterio-venous [O₂] gradient to calculate pulmonary blood flow

$$\text{PBF} = \frac{\text{VO}_2}{(\text{CaO}_2 - \text{CvO}_2)} = \frac{250 \text{ mL/min}}{(200 \text{ mL/L} - 150 \text{ mL/L})} = 5 \text{ L/min}$$

- Technique – VO₂ = slope of tracing obtained from patient rebreathing O₂ from Benedict-Roth spirometer through soda-lime absorber; CaO₂ obtained from arterial blood (arterial line); CvO₂ from MVB (PA catheter)

Renal blood flow (RBF) measurement:

- RBF is 1200 mL/min
- Principle and technique:
 - o Renal plasma flow (RPF) is determined by calculating the renal clearance of a substance that undergoes complete glomerular filtration and tubular secretion such that NONE remains in the renal venous blood (I.e. 100% renal excretion)
 - o Para-aminohippuric acid (PAH) is thus used to calculate RPF:
 - At low plasma [PAH], all plasma-perfusing, filtering and secreting parts of the kidney virtually clear it completely → 90% PAH excreted in urine

- As a result, the renal clearance of PAH (C_{PAH}) is actually an underestimate of “Total” RBF $\rightarrow C_{PAH}$ is thus the “Effective” RPF

$$\text{“Total” RPF} = \frac{\text{ERPF}}{\text{Extraction ratio}} = \frac{625 \text{ mL/min}}{0.9} = 700 \text{ mL/min}$$

Note: RPF is not clinically measured with PAH as it often underestimates it:

- (i) Disease states and other organic acids interferes with PAH tubular secretion
- (ii) When the PAH secretory mechanism is saturated (such as in high plasma [PAH]), PAH is no longer 100% excreted (I.e. $\downarrow$ secretion of PAH) $\rightarrow$ thus, C_{PAH} does not equal RPF (in fact, it approaches GFR)

- Renal Blood Flow (RBF):

$$\text{“Renal blood flow”} = \frac{\text{Effective renal plasma flow}}{1 - \text{blood haematocrit}} = 1200 \text{ mL/min}$$

Hepatic blood flow (HBF) measurement:

- HBF is 1.5 L/min $\rightarrow$ 300-500 mL from hepatic artery and 1000-1200 mL from portal vein
- Principle – Based on “Fick’s principle” (see above) $\rightarrow$ uses removal of indocyanine green (ICG) dye from hepatic circulation (as it has 100% biliary excretion and lacks enterohepatic recycling) and arterio-venous [ICG] gradient to calculate HBF
- Techniques:
 - (i) Single ICG bolus technique $\rightarrow$ single IV bolus of ICG is given and venous samples are collected every 2 minutes for 14 minutes. Concentration-time delay curves are analysed to determine its clearance

$$\text{Hepatic blood flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC of conc. vs time}}$$

Extraction ratio of ICG is 0.74

- (ii) Continuous ICG infusion technique $\rightarrow$ ICG infused for 20 mins to achieve steady-state/equilibrium (I.e. infusion rate = hepatic uptake) $\rightarrow$ samples taken simultaneously from any peripheral artery ($\approx$ hepatic arterial [ICG]) and a cannulated hepatic vein (= hepatic vein [ICG])

$$\text{Hepatic blood flow} = \frac{\text{Clearance}}{\text{Extraction ratio}}$$

$$\text{Clearance} = \frac{\text{Infusion rate}}{\text{Hepatic arterial [ICG]}}$$

$$\text{Extraction ratio} = \frac{(\text{Hepatic arterial [ICG]} - \text{Hepatic venous [ICG]})}{\text{Hepatic arterial [ICG]}}$$

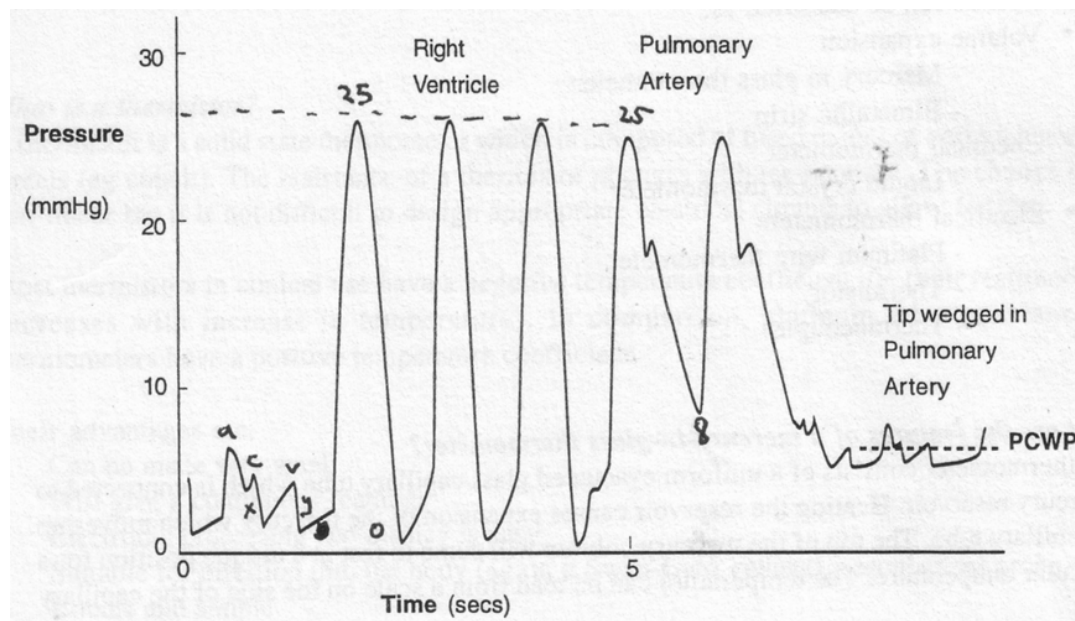
Skin blood flow measurement:

- Use fluorescent ICG $\rightarrow$ visualise with near-IR video system

Aside: Swan-Ganz Catheter and Central Venous Pressure

Pulmonary arterial catheter (aka. Swan-Ganz catheter):

- A balloon-tipped catheter inserted into a thoracic central vein → it is “flow-directed” into the pulmonary artery (as blood flow through right-side of heart → PA) directs catheter
- Uses:
 - Continuous monitoring of:
 - (i) PA pressures (systolic, diastolic, mean)
 - (ii) Body temperature
 - Intermittent monitoring of:
 - (i) PAOP or PCWP (as an index of LV preload)
 - Inflation of balloon at catheter tip occludes a branch of PA → flow ceases → trace obtained similar to LAP trace
 - Mean PCWP/PAOP $\approx$ LAP → assuming a normal MV, LV compliance and AW pressure, it $\approx$ LVEDP → correlates with LVEDV (index of LV preload)
 - (ii) C.O. measurement (using thermodilution technique – see above)
 - (iii) Haemodynamic parameters (SVRI, PVRI, CI, SV, Etc.)
 - (iv) MVB sampling for SvO₂
- PA catheter tracing (with wedging):



Central venous pressure (CVP) measurement:

- Significance of CVP:
 - It approximates RAP, which determines RV EDV pressure (RV filling/preload)
 - In healthy hearts, RV and LV performance parallels each other → so LV filling/preload $\approx$ RV filling/preload
- Technique:
 - Place catheter into a central vein (IJV or SCV) so tip lies above or at the junction of SVC and RA

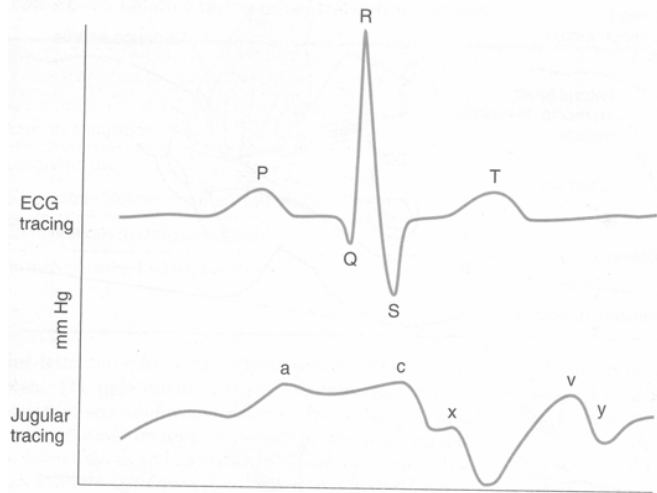
Aside – Uses of CVC:

- (i) Administer fluids to treat shock and hypovolaemia
- (ii) Infusion of caustic drugs and TPN
- (iii) IVC access in pts with difficult peripheral cannulation
- (iv) Monitor CVP

- Patient is positioned horizontally

- CVP is measured using either an electronic pressure transducer or a H₂O column:
 - Measurement system zeroed at mid-axillary line → represents RA
 - Since the CVC tip is exposed to intra-thoracic pressure, CVP will vary with inspiration/expiration → thus CVP is measured at end-expiration
 - Electronic pressure transducer system permits continuous recording of CVP and its waveform

- CVP waveform:



- a-wave = atrial contraction
- c-wave = TV elevation during early ventricular contraction
- v-wave = venous return against closed TV
- x-descent = downward displacement of TV during systole
- y-descent = opening of TV during diastole

VI. REGIONAL CIRCULATION

- (a) *To describe the relationship between organ blood flow and demand, and the role of autoregulation.*

Resting blood flow and O₂ consumption of various organs:

Region	Resting Blood Flow		Resting O ₂ consumption		
	mL/min (% C.O.)	mL/100 g/min	mL/min (% total O ₂ consumption)	mL/100 g/min	A-V O ₂ difference (mL/L)
Liver	1500 (30%)	60	50 (20%)	2	34
Kidneys	1200 (20%)	420	18 (7%)	6	14
Skeletal muscle	1200 (20%)	3	50 (20%)	0.2	60
Brain	750 (15%)	54	45 (18%)	3.3	62
Skin	500 (10%)	13	12 (5%)	0.3	25
Heart	250 (5%)	85	29 (12%)	9.7	114
Whole body	5000-6000 (100%)	9	250 (100%)	0.4	50

Determinants and control of organ blood flow:

Organ blood flow is determined by – (i) perfusion pressure to organ, and (ii) resistance of its vascular bed:

$$\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$$

$$\text{Organ blood flow} = \frac{\text{Mean arterial pressure}}{\text{Organ vascular resistance}}$$

As all systemic vascular beds are exposed to the same perfusion pressure (or MAP), the distribution of C.O. to each individual organ is therefore determined by the state of vascular SM tone in its supplying arteriolar (resistance) vessels (or organ vascular resistance)

Factors that influence arteriolar SM tone (or organ vascular resistance), and thus control of organ blood flow includes:

(1) Local factors:

- (a) Local myogenic control (aka. “pressure autoregulation”)
 - o Organ blood flow is kept constant over a wide range of arterial BP → this is caused by compensatory changes in the organ’s arteriolar resistance in response to changes in arterial BP within that range
 - o Mechanism – ↑ arterial BP causes ↑ arteriolar wall stretching → arteriolar SM respond by contracting and ↑ arteriolar tone → this results in vasoconstriction and ↑ arteriolar resistance → offsets ↑ local blood flow a/w ↑ arterial BP (the opposite outcome occurs with ↓ arterial BP)

Important to note – This effect is prominent in brain and kidneys

- (b) Local metabolic control (aka. “metabolic autoregulation”)
 - o Organ blood flow is varied in accordance to the metabolic needs of the organ
 - o Mechanism – ↑ organ metabolic activity leads to ↑ local production of a “mediator” (pCO₂, H⁺, K⁺, adenosine, Pi, lactic acid, pyruvate, NO, temperature) and ↓ pO₂ → causes arteriole SM to relax and ↓ arteriolar tone → results in vasodilation and ↓ arteriolar resistance → ↑ organ blood flow

Important to note – This effect is prominent in the heart, brain and skeletal muscles

- (c) Local tissue pressure control
 - o Organ blood flow is affected by extravascular compression by ISF
 - o Mechanism – $\uparrow$ organ blood flow produces $\uparrow$ ISF that compresses the arterioles from the outside $\rightarrow$ generates $\uparrow$ arteriolar resistance that limits blood flow

Important to note – This effect is prominent in organs with tight capsules (esp kidneys)

- (d) Local tissue vasoactive chemical control
 - o (i) Glandular cells (esp salivary, sweat and intestinal glands) produce kallikrein when “active” $\rightarrow$ converts inactive kininogens to active kinins (esp bradykinin) that relaxes arteriolar SM and $\downarrow$ arteriolar tone $\rightarrow$ vasodilation and $\uparrow$ blood flow
 - o (ii) Endothelial cells produce vasoactive substances – PCI-2 and NO are vasodilators, while ET-1 is a vasoconstrictor
 - o (iii) Activated platelets produce TXA-2, which causes vasoconstriction

(2) Systemic factors:

- (a) Extrinsic SNS control
 - o Arterioles have profuse SNS supply $\rightarrow$ NAd from nerve endings act on α 1-adrenoceptors to cause vasoconstriction (and β 2-adrenoceptors to cause vasodilation – but effect is weaker!)
 - o Due to the tonic SNS outflow from medullary vasomotor centres, arterioles have a basal level of vasoconstriction $\rightarrow$ the degree of basal vasoconstriction (and arteriolar resistance) can be varied by altering SNS outflow

Important to note – This is prominent in skin, kidneys and GIT

- o Of note, skeletal muscle has “SNS cholinergic vasodilator” supply under cortical control $\rightarrow$ causes vasodilation with exercise to $\uparrow$ skeletal muscle blood flow
- (b) Extrinsic PNS control
 - o PNS control of arterioles is less important $\rightarrow$ vessels of external genitalia have dual ANS supply with PNS dilator nerves and SNS constrictor supply; PNS activation in heart, brain and lungs have an uncertain role
- (c) Extrinsic hormonal control
 - o (i) Adrenaline (from adrenal medulla) $\rightarrow$ effect on organ blood flow depends on the relative % of α 1- and β 2-adrenoceptors present in the arteriole

For example:

- Heart and skeletal muscle $\rightarrow$ arterioles have $\uparrow$ proportion of β 2-adrenoceptors $\rightarrow$ Adr causes vasodilation and $\uparrow$ blood flow
- GIT and skin $\rightarrow$ arterioles have $\uparrow$ proportion of α 1-adrenoceptors $\rightarrow$ Adr causes vasoconstriction and $\downarrow$ blood flow

- o (ii) AII (from RAAS) $\rightarrow$ vasoconstriction (via AT2R)
- o (iii) ADH (from posterior pituitary) $\rightarrow$ vasoconstriction (via V1R)
- o (iv) ANP (from RA) $\rightarrow$ vasodilation (via ANPR)

Autoregulation:

“Autoregulation” $\rightarrow$ an organ’s ability to regulate its own blood supply so it receives an adequate amount of blood flow for its functions

Mechanism – Dependent on various “intrinsic” mechanisms that include:

- (1) Pressure autoregulation (aka. local myogenic control)
 - o Organ blood flow is kept constant over a wide range of arterial BP $\rightarrow$ this is caused by compensatory changes in the organ’s arteriolar resistance in response to changes in arterial BP within that range

- Mechanism – $\uparrow$ arterial BP causes $\uparrow$ arteriolar wall stretching $\rightarrow$ arteriolar SM respond by contracting and $\uparrow$ arteriolar tone $\rightarrow$ this results in vasoconstriction and $\uparrow$ arteriolar resistance $\rightarrow$ offsets $\uparrow$ local blood flow a/w $\uparrow$ arterial BP (the opposite outcome occurs with $\downarrow$ arterial BP)
- This is prominent in the brain and kidneys
- (2) Metabolic autoregulation (aka. local metabolic control)
 - Organ blood flow is varied in accordance to the metabolic needs of the organ
 - Mechanism – $\uparrow$ organ metabolic activity leads to $\uparrow$ local production of a “mediator” (pCO_2 , H^+ , K^+ , adenosine, Pi, lactic acid, pyruvate, NO, temperature) and $\downarrow$ pO_2 $\rightarrow$ causes arteriole SM to relax and $\downarrow$ arteriolar tone $\rightarrow$ results in vasodilation and $\downarrow$ arteriolar resistance $\rightarrow$ $\uparrow$ organ blood flow
 - This is prominent in the heart, brain and skeletal muscles
- (3) “Tissue pressure” theory?
 - Organ blood flow is affected by extravascular compression by ISF
 - Mechanism – $\uparrow$ organ blood flow produces $\uparrow$ ISF that compresses the arterioles from the outside $\rightarrow$ generates $\uparrow$ arteriolar resistance that limits blood flow
 - This is prominent in organs with tight capsules (esp kidneys)

Important to note – Autoregulation is NOT dependent on any “extrinsic” mechanisms (Ie. neural or humoral factors)

Most tissues exhibit autoregulation (esp heart, brain and kidney) $\rightarrow$ however, there are tissues where pressure autoregulation is absent:

- (1) Uterine circulation during pregnancy $\rightarrow$ vascular bed of pregnant uterus is fully dilated, such that uterine blood flow is entirely pressure-dependent

Implications – $\downarrow$ BP (Ie. neuraxial block, LSCS) results in $\downarrow$ UBF, which can impair foetal oxygenation (although UBF can be halved before any foetal desaturation occurs $\rightarrow$ “safety margin”)

- (2) Hepatic portal circulation $\rightarrow$ venous drainage from bowel in the liver is entirely pressure-dependent

Note – Hepatic arterial circulation is “autoregulated” (See below)

(b) ***To describe the features of the coronary circulation and to explain the clinical significance of these.***

Overview of the coronary circulation:

Blood supply to the myocardium comes from 2 coronary arteries that arise from the aortic root behind the cusps of the aortic valve:

- (1) Left coronary artery → divides into (i) left anterior descending and (ii) left circumflex → supplies LA and most of LV
- (2) Right coronary artery → supplies RA and RV

Important to note – Inferior wall of LV is supplied by RCA in 50% of pop'n (RCA or right dominant), and by LCA in 20% of pop'n (LCA or left dominant)

Venous drainage from coronary circulation reenters the systemic circulation via:

- (1) Coronary sinus → most venous blood from coronary circulation (90%) – esp from LV – drains into the RA via the coronary sinus

Note – Coronary sinus blood has pO_2 20 mmHg → b/c of very high myocardial O_2 extraction ratio (55-65%)

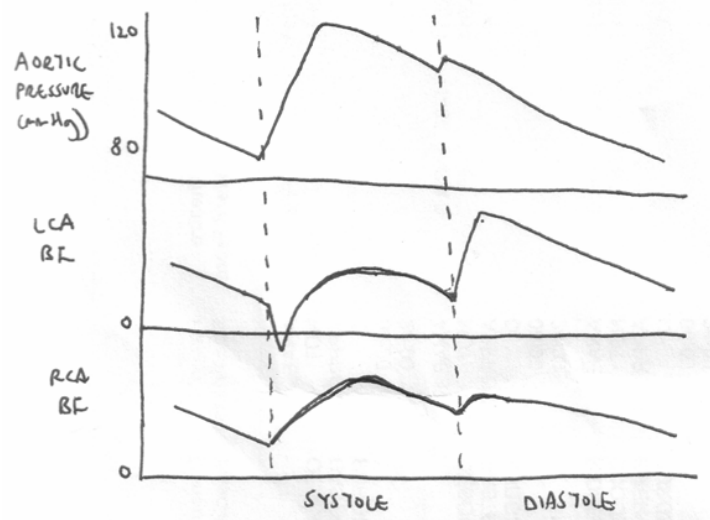
- (2) Anterior cardiac veins → most venous blood from RV drains into RA via the anterior cardiac veins
- (3) Thebesian veins → small amounts of venous blood drains into all heart chambers via the thebesian veins

Coronary blood flow (CorBF):

“CorBF” → 250 mL/min (or 5% of total C.O.) or 85 mL/100g/min at rest

CorBF varies in different parts of the cardiac cycle and b/t left and right coronary arteries:

- (i) Left coronary artery blood flow to LV is “intermittent” → blood flow occurs mainly during diastole (cf. during systole), and blood flow during early systole can cease and reverse (esp in subendocardium) → this is b/c LV systolic pressures are high (120 mmHg) and can compress the coronary vessel
- (ii) Right coronary artery blood flow to RV is “pulsatile” → blood flow occurs in both phases of the cardiac cycle (but slightly higher during systole) → this is b/c RV systolic pressures are lower (25 mmHg), so the differences in blood flow b/t systole and diastole are much less
- (iii) Majority of total coronary blood flow (80%) occurs during diastole where there is no compression of the coronary vessels



Note – LV receives much more blood flow than RV b/c it has a much bigger muscle mass!

Implications – Flow is rate-dependent:

- With tachycardia → despite ↓ diastole time in each cardiac cycle, CorBF is not compromised as there is compensatory ↑ in blood flow 2° to metabolic autoregulation a/w ↑ metabolic activity
- With bradycardia → despite ↑ diastole time in each cardiac cycle, CorBF is not excessive as there is compensatory ↓ in blood flow 2° to metabolic autoregulation a/w ↓ metabolic activity

CorBF is determined by – (i) Coronary perfusion pressure and (ii) Coronary vascular resistance

$$CBF = \frac{CPP}{CVR}$$

(1) Coronary perfusion pressure (CPP) → driving pressure for coronary blood flow

- CPP acts as a “Starling Resistor” (Ie. perfusion pressure for blood flow normally depends on the arterial-venous pressure difference, but can become dependent on the difference b/t arterial pressure and pressure outside the vessels instead when there is external vascular compression present) → thus CPP depends on 3 factors:
 - (i) Arterial (aortic root) pressure
 - (ii) Intraventricular pressure
 - (iii) Coronary sinus (or RA) pressure

Note – CPP can be determined for each ventricle during each phase of cardiac cycle:

- LV (systole) → $CPP = ASP - LVSP = 120 - 120 = \mathbf{0 \text{ mmHg}}$
- LV (diastole) → $CPP = ADP - RAP = 80 - 5 = \mathbf{75 \text{ mmHg}}$
- RV (systole) → $CPP = ASP - RVSP = 120 - 25 = \mathbf{95 \text{ mmHg}}$
- RV (diastole) → $CPP = ADP - RAP = 80 - 5 = \mathbf{75 \text{ mmHg}}$

- Since most CorBF occurs during diastole (esp in LV), then CPP is estimated as follows:

$$CPP = ADP - LVDP \text{ (or RAP)}$$

Note: ADP = Aortic root diastolic pressure
LVDP = LV diastolic pressure
RAP = Right atrial pressure (= coronary sinus pressure)

Important to note – LVDP and RAP are *much smaller* than ADP → thus, ADP can be used a general measure of CPP (as $CPP \approx ADP$)

Note – Measurement of peripheral ADP is an index of CPP → but this is difficult to accurately obtain with non-invasive and invasive methods!

(2) Coronary vascular resistance (CVR) → resistance to coronary blood flow

- Coronary arteriolar tone (and CVR) at rest is high → this allows for ↑ in CorBF (2° to coronary vasodilation) when myocardial O₂ demands ↑
- CVR is affected by:
 - (a) Local (autoregulatory) mechanisms
 - (i) Metabolic autoregulation (MAJOR) – ↑ cardiac metabolic activity leads to ↑ production of local metabolites (CO₂, H⁺, K⁺, adenosine, lactic acid, pyruvate, NO, Pi) and ↓ pO₂ → causes coronary arteriolar vasodilation and ↓ CVR → ↑ CorBF

- (ii) Pressure autoregulation (minor) – CorBF is kept constant b/t ADP of 60-180 mmHg via a “myogenic mechanism” (See above)
- (b) Extrinsic (ANS) mechanisms
 - (i) SNS control
 - NAd and Adr directly act on both α 1-adrenoceptors (vasoconstricting effect) and β 2-adrenoceptors (vasodilating effect) in coronary vessels → net effect is vasoconstriction and ↓ CorBF (as α 1 receptors >> β 2 receptors)
 - NAd and Adr indirectly ↑ HR and myocardial contractility, which ↑ metabolic activity → causes vasodilation and ↑ CorBF (as per metabolic autoregulation) → this overrides the direct effects
 - (ii) PNS control
 - ACh directly act on mAChR to cause vasodilation and ↑ CorBF
 - ACh indirectly ↓ HR, which ↓ metabolic activity → causes vasoconstriction and ↓ CorBF (as per metabolic autoregulation) → this overrides the direct effects
- (c) Extravascular compression
 - Vessel are compressed with ↑ intraventricular pressure → ↓ vessel calibre and ↑ CVR → ↓ CorBF

Myocardial extraction and coronary blood flow:

“Myocardial O₂ consumption” → 8-10 mL/100g/min (or 30 mL/min (12% of total O₂ consumption)) at rest

“Myocardial O₂ extraction” → very high at rest (extraction ratio = 55-65%), such that AV O₂ difference = 11 mL/dL and coronary venous O₂ content = 5 mL/dL

Important to note – Myocardial O₂ extraction is very high b/c CorBF is low relative to myocardial O₂ consumption → thus, the heart needs to extract heaps of O₂ from each unit of blood flow

Important to note – Myocardial O₂ extraction remains constantly very high at rest → this means that when there is ↑ myocardial O₂ demand (I.e. exercise), CorBF must ↑ to provide the heart with additional O₂ (cf. ↑ myocardial O₂ extraction). In fact, CorBF ↑ 4-5x (up to 1000-1250 mL/min), mainly during diastole (esp in LV), due to effects of metabolic autoregulation

Myocardial O₂ balance:

Myocardial O ₂ supply	Myocardial O ₂ demand
(1) CorBF → determined 1 ^o ly by CPP ($\approx$ ADP), but also CVR (autoregulation and ANS control)	(1) Ventricular wall tension → determined by preload (EDV/EDP) and afterload (SVR)
(2) O ₂ content of arterial blood (CaO ₂) → determined 1 ^o ly by [Hb] and SaO ₂	(2) HR → ↑ HR means both (i) ↓ supply (as perfusion is inversely related to HR) and (ii) ↑ demand (as ↑ MRO ₂)
	(3) Myocardial contractility

(c) *To describe autoregulation in the cerebral circulation and the factors that may affect it.*

Overview of the cerebral circulation:

“Cerebral blood flow” (CBF) → 750 mL/min (15% of C.O.) or 50-54 mL/100g/min at rest

“Cerebral metabolic rate of O₂ consumption” (CMRO₂) → 3-3.5 mL/100g/min (or 50 mL/min (20% of total O₂ consumption)) at rest

Important to note – Cerebral function is entirely dependent on oxidative phosphorylation of glucose to generate energy, and thus requires a continuous and uninterrupted supply of blood → if there is prolonged interruption of blood supply, cerebral ischaemia occurs as the brain is very sensitive to hypoxia → this is b/c:

- (1) Brain has a very high metabolic rate (or CMRO₂) → although brain weighs 1400 g (2% of body weight), it uses 20% of total resting O₂ consumption!
- (2) Brain lacks substrate storage (O₂ and glucose)

Factors that determine cerebral blood flow (CBF):

CBF is determined by – (i) Cerebral perfusion pressure and (ii) Cerebral vascular resistance

$$CBF = \frac{CPP}{CVR}$$

(1) Cerebral perfusion pressure (CPP) → driving pressure for cerebral blood flow

- CPP acts as a “Starling Resistor” (Ie. perfusion pressure for blood flow normally depends on the arterial-venous pressure difference, but can become dependent on the difference b/t arterial pressure and pressure outside the vessels instead when there is external vascular compression present) → thus CPP depends on 3 factors:
 - o (i) Mean arterial pressure
 - o (ii) Central venous pressure
 - o (iii) Intracranial pressure

$$CPP = MAP - CVP \text{ (or ICP)} \quad * \text{Nb. Subtract which ever value is greatest (CVP or ICP)}$$

Important to note – ICP and CVP are *much smaller* than MAP → thus, MAP can be used as a general measure of CPP (as $CPP \approx MAP$), EXCEPT during pathological conditions (Ie. ↑ ICP, ↑ CVP or ↓ MAP)

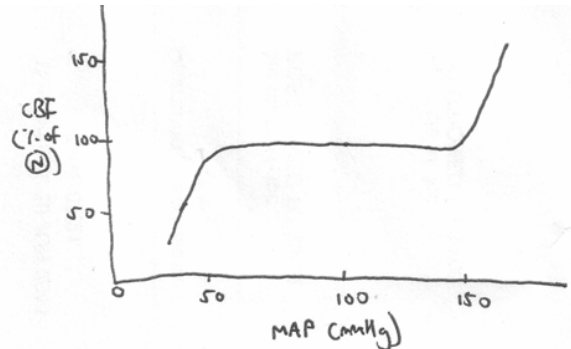
Note – Measurement of MAP is easier, less invasive and more continuous (cf. ICP and CVP)

- Control of MAP (and thus CPP) is mainly determined by the “arterial BRR” and “ANS outflow” from the medullary vasomotor centre (Ie. ↓ MAP is detected by high-pressure baroreceptors in carotid sinus and aortic arch, which reflexly inhibit arterial BRR → ↑ SNS outflow (and ↓ PNS outflow) → ↑ HR, ↑ myocardial contractility, ↑ SVR and ↑ venous return to restore MAP (and CPP for cerebral blood flow to occur))

Note – “CNS ischaemic response” (aka. Cushing response) → extreme cerebral hypoxia due to severe hypotension (BP < 50 mmHg) triggers a massive SNS outflow from ischaemic medulla in last attempt to maintain BP and CPP (and CBF/O₂ supply)

(2) Cerebral vascular resistance (CVR) → resistance to cerebral blood flow → determined by:

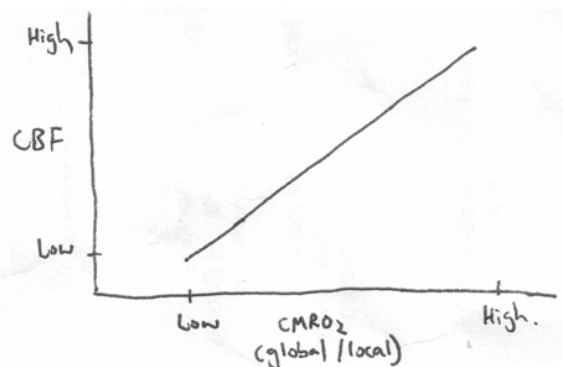
- (a) Pressure autoregulation (aka. local myogenic control)
 - CBF is kept constant within a wide-range of MAP (50-150 mmHg) despite fluctuations in MAP within this range
 - Mechanism – $\uparrow$ arterial BP causes $\uparrow$ arteriolar wall stretching $\rightarrow$ arteriolar SM respond by contracting and $\uparrow$ arteriolar tone $\rightarrow$ this results in vasoconstriction and $\uparrow$ arteriolar resistance $\rightarrow$ offsets $\uparrow$ local blood flow a/w $\uparrow$ arterial BP (the opposite outcome occurs with $\downarrow$ arterial BP)



Note – Pressure autoregulation curve is shifted under certain circumstances:

- Chronic HTN, $\uparrow$ ICP, acute SNS stimulation $\rightarrow$ shifts curve to right (but MAP plateau range and slope remains unchanged) $\rightarrow$ so $\downarrow$ in MAP can easily be a/w $\downarrow$ CBF
- Neonates $\rightarrow$ curve shifts to left, has a narrower MAP plateau range (30-90 mmHg) and steeper slope $\rightarrow$ this allows them to tolerate physiologically lower BP (but are susceptible to $\uparrow$ CBF with higher BPs)

- (b) Metabolic autoregulation (aka. local metabolic control)
 - “Flow-metabolism coupling” $\rightarrow$ $\uparrow$ cerebral metabolic activity (or CMRO_2) is a/w an appropriate $\uparrow$ in CBF to meet its metabolic demands
 - Mechanism – $\uparrow$ cerebral activity is a/w $\uparrow$ metabolism $\rightarrow$ produces local metabolites (Eg. H^+ , K^+ , adenosine, NO, Etc.) with vasodilatory properties $\rightarrow$ relaxes arteriolar SM tone and $\uparrow$ vasodilation $\rightarrow$ $\downarrow$ CVR $\rightarrow$ $\uparrow$ CBF



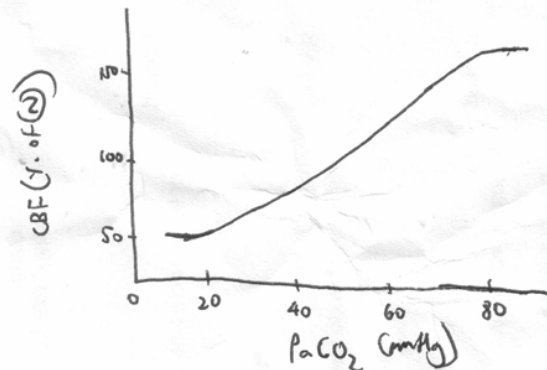
- This process influences both:
 - (i) Regional CBF $\rightarrow$ moment-to-moment regulation of regional CBF in the brain occurs even through global CBF remains constant (Ie. lifting arms redistributes $\uparrow$ CBF to motor cortex)
 - (ii) Global CBF $\rightarrow$ global $\uparrow$ in CMRO_2 (Ie. generalised seizures) is a/w $\uparrow$ global CBF, while global $\downarrow$ in CMRO_2 (Ie. volatile anaesthesia at < 1 MAC, or hypothermia) is a/w $\downarrow$ global CBF

Important to note – Metabolic autoregulation (and “flow-metabolism” coupling) plays a more vital role in regional distribution of CBF (cf. control of global CBF)

- (c) Chemical factors

○ (i) CO₂ (IMPORTANT factor)

- At normal MAP and b/t a pCO₂ range of 20-80 mmHg, CBF is directly proportional to pCO₂ → CBF ↑ 2-4% for every ↑ mmHg pCO₂
- Mechanism – CO₂ diffuses rapidly across BBB → ↑ [H⁺] in brain ECF → causes vasodilation of cerebral arterioles and ↑ CBF



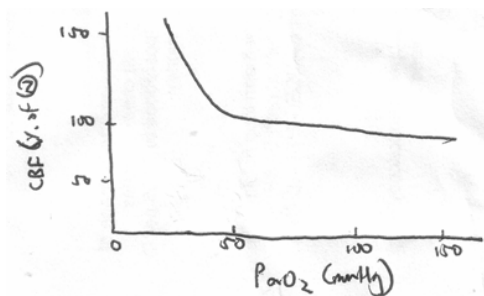
Important to note – Severe hypo- or hypertension can abolish cerebrovascular response to pCO₂

Important to note – Δ in CBF caused by Δ in pCO₂ is TEMPORARY only → this is b/c the Δ in brain ECF pH a/w sustained Δ in pCO₂ is diminished over time as HCO₃⁻ equilibrates across the BBB → thus, brain ECF pH and Δ in CBF normalise within 4-12 hrs (despite Δ pCO₂ being sustained). Importantly, any sudden return of pCO₂ back to “normal” causes a Δ in CBF in the opposite direction

Clinical relevance – Hyperventilation to ↓ pCO₂ is useful to ↓ ICP 2° to ↓ cerebral blood volume (or CBF) → the effect is rapid, potent, reliable, easily controlled and monitored → BUT for the reasons described above, it should only be used acutely (I.e. removal of IC SOL). If used chronically, excessive ↑ ICP 2° to ↑ CBV (or CBF) can occur if pCO₂ is allowed to ↑ due to compensatory mechanisms described above

○ (ii) O₂

- Within physiological limits, pO₂ does NOT affect CBF → BUT when pO₂ < 50 mmHg, there is a significant ↑ CBF as pO₂ ↓ (I.e. CBF doubles when pO₂ ↓ to 30 mmHg)
- Mechanism – Tissue hypoxia leads to lactic acidosis → ↑ [H⁺] in brain ECF → causes vasodilation of cerebral arterioles and ↑ CBF



Important to note – The sudden ↑ in CBF at pO₂ < 50 mmHg is the result of the sigmoidal shape of the OHDC → as pO₂ ↓, O₂ content of blood does not significantly ↓ UNTIL pO₂ is < 50-60 mmHg (I.e. steep part of curve) → the large ↓ blood O₂ content means ↓ O₂ delivery to the brain, which causes tissue hypoxia → triggers reflex arteriolar vasodilation and ↑ CBF to restore cerebral O₂ delivery

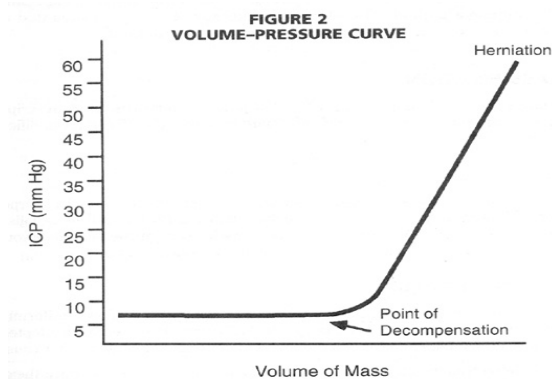
- (d) Temperature
 - o Each 1°C ↓ in body temperature results in a 7% ↓ in CMRO₂ → leads to ↓ CBF
 - o Mechanism – Related to metabolic autoregulation (see above)
- (e) Nervous control
 - o ANS control of cerebrovascular tone (or CVR) is minimal (5-10% only)

Important to note – ANS control is very important in controlling CBF → BUT it mainly affects CPP (See above), rather than CVR!

Cerebral blood flow and ICP:

Remember:

- “Munro-Kellie Doctrine” → In adults, the rigid and closed cranial vault forms a FIXED brain volume that contains – (1) Brain parenchyma (80%, 1400 g), (2) CSF (10%; 75 mL) and (3) Cerebral blood and vessels (10%; 75 mL) → thus, any change in volume of any one of these components will alter the volume of one or more of the other components of cranial contents
- ICP is determined by the volume of each of these 3 cranial components such that a Δ in volume of any one component will affect ICP as follows:



Note – This figure “pressure volume-relationship” demonstrates “Intracranial Elastance” (plots Δ ICP against Δ intracranial volume), rather than “Intracranial compliance”

- Within the rigid, closed and fixed volume cranial vault → brain parenchyma and CSF are generally non-compressible, whereas cerebral blood vessels are easily compressed → thus, in the event of ↑ ICP due to alteration in volume of one of the components, there are compensatory mechanisms invoked to minimise it:
 - o (i) Initially, there is Δ in CSF distribution and flow → CSF is displaced to spinal subarachnoid space and/or resorption rate ↑’s
 - o (ii) Later on → ↓ in cerebral blood volume 2° to ↓ CBF a/w ↑ ICP → leads to cerebral ischaemia
 - o (iii) In very late stages → “decompensation point” where all possible structural displacement is exhausted and ↓ in cerebral tissue volume occurs (I.e. brain herniation and death)

↑ in CBF causes ↑ cerebral blood volume, resulting in results in ↑ ICP → this can be minimised by:

- (1) Head-up tilt → ↓ hydrostatic effects on CPP and ↓ CVP → ↓ CBF
- (2) Ensure no obstruction to venous drainage → keeps CVP low → ↓ CBF
- (3) Avoid cerebral vasodilators (Eg. halothane) → keeps CVR high → ↓ CBF
- (4) Hyperventilation → ↓ pCO₂, which keeps CVR high → ↓ CBF
- (5) Mannitol or hypertonic saline → ↓ brain water content → ↓ ICP
- (6) Controlled hypotension → ↓ CPP → ↓ CBF

Important to note – “Cushing reflex” → ↑ ICP causes reflex ↑ MAP and ↓ HR. This is b/c ↑ MAP maintains CBF in presence of ↑ ICP; arterial BRR is triggered by ↑ BP, which causes reflex inhibition of SNS outflow and ↓ HR

(d) ***To describe the renal circulation and to explain its significance in maintaining renal function.***

Overview of the renal circulation:

“Renal blood flow” (RBF) → 1200 mL/min (20% of C.O) or 420 mL/100g/min at rest → of which the majority goes to the cortex (95% of RBF – cf. medulla, which receives 5% of RBF)

Note – Kidneys are 150 g (only 1% body weight) → BUT have the HIGHEST blood flow per gram of tissue in body (at 420 mL/100g/min) at rest)

“Renal O₂ consumption” → 6 mL/100g/min (or 18 mL/min (7% of total O₂ consumption)) at rest

“Renal O₂ extraction” → LOWEST in the body (with AV O₂ difference of 1.4 mL/dL) b/c RBF (and renal O₂ delivery) vastly exceeds renal O₂ metabolic demand by 10X → the level of O₂ extraction, however, varies on the part of the nephron:

- Cortex → Low O₂ extraction ratio because (i) Not very metabolic (PO₂ 50 mmHg) and (ii) very ↑ blood flow (10x more than medulla)
- Medullary → High O₂ extraction ratio because (i) Very metabolic (need to maintain osmotic gradient in medullary interstitium with Na⁺ reabsorption in TAL; PO₂ 15 mmHg) and (ii) very ↓ blood flow

Important to note:

- Kidneys are ONLY organ where its metabolic demands (or O₂ consumption) is NOT a determinant of its blood flow → for instance, in spite of its high metabolic demands, its RBF (and O₂ delivery) is in excess of what it needs (by 10X)
- Rather, the purpose of its excessive RBF is to be able to produce large amounts of glomerular ultrafiltrate for urinary excretion of waste products!

Important to note – Despite O₂ delivery (and RBF) being in excess of O₂ demand, the kidneys are susceptible to ischaemic damage (esp the medulla) if there is any large ↓ in total O₂ delivery (and RBF) → this is because:

- (1) RBF is autoregulated to maintain GFR and Na⁺ balance, rather than to meet renal metabolic demand
- (2) Renal metabolic rate has little autoregulatory influence over peritubular capillary blood flow
- (3) Counter-current exchange of O₂ in vasa recta ↓ peritubular capillary PO₂ as they descend into the medulla
- (4) ↓ blood flow in medulla (by 10X cf. cortex)
- (5) Medulla has the highest metabolic demand (cf. cortex) due to Na⁺ reabsorption to maintain the ↑ medullary interstitial osmotic gradient

Control of renal blood flow (RBF):

Control of RBF is determined by the calibre of its main resistance vessels:

- (i) Afferent arteriole – Constriction → ↓ RBF; Dilation → ↑ RBF
- (ii) Efferent arteriole – Constriction → ↓ RBF; Dilation → ↑ RBF

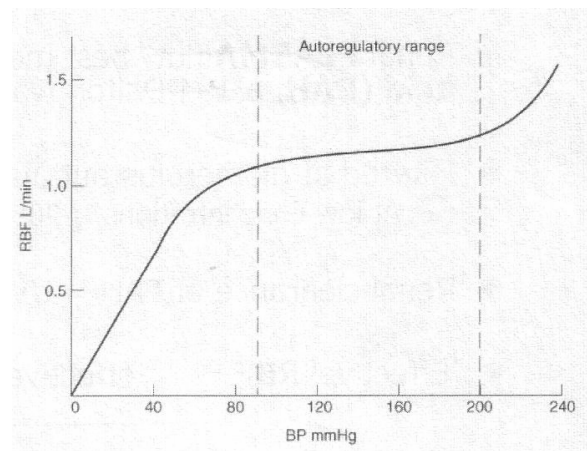
The calibre of its resistance vessels is under the influence of:

(1) Intrinsic (autoregulation):

- RBF is autoregulated and kept constant within a MAP range of 75-170 mmHg via changes in calibre (and resistance) of the AFFERENT arteriole of the kidney

Note:

- Efferent arteriole is NOT involved in autoregulation!
- Autoregulation of GFR and RBF can be overridden by external influences (Eg. hormones and SNS neurons), even when renal perfusion pressure is between MAP 75-170 mmHg!



- Mechanisms:
 - (a) Myogenic regulation
 - VSMC of the afferent arterioles contract in response to vessel wall stretching caused by $\uparrow$ renal perfusion pressure $\rightarrow$ causes afferent arteriolar vasoconstriction $\rightarrow$ normalise RBF
 - (b) Tubuloglomerular feedback
 - Intrinsic mechanism that regulates 1^oly GFR (and RBF 2^oly) $\rightarrow$ inherent to all nephrons within the kidney $\rightarrow$ it ensures that each nephron has a relatively constant rate of ultrafiltrate delivered to its DCT (whatever the GFR may be) by controlling its glomerular blood flow via a $-ve$ feedback reflex effect on the afferent arteriolar tone
 - It has a rapid effect (within seconds) $\rightarrow$ RAAS has a long-term role by adjusting the mechanism's set-point

Mechanism:

- Macula densa (within EDCT in JGA) indirectly measures GFR (and RBF) by gauging the rate of ultrafiltrate delivery to it $\rightarrow$ achieves this by measuring the ionic composition of tubular fluid (Na^+ and Cl^-) using a NKCC2 co-transporter such that:
 - (i) $\uparrow [NaCl]$ $\rightarrow$ means $\uparrow$ UF delivery to MD $\rightarrow$ $\uparrow$ GFR (and RBF)
 - (ii) $\downarrow [NaCl]$ $\rightarrow$ means $\downarrow$ UF delivery to MD $\rightarrow$ $\downarrow$ GFR (and RBF)
- Through this "sensor mechanism", the macula densa then sends a feedback signal through the JGA to the glomerulus to regulate GFR (and RBF) by altering the tone of the renal afferent arteriole as follows:
 - (i) $\uparrow [NaCl]$ or GFR causes the macula densa to:
 - (a) Release Adenosine $\rightarrow$ binds A1 receptors on Extraglomerular mesangial cells $\rightarrow$ causes $\uparrow$ in IC $[Ca^{2+}]$ $\rightarrow$ signal transmission across gap junctions to induce afferent arteriolar vasoconstriction $\rightarrow$ $\downarrow$ GFR (and RBF)
 - (b) $\downarrow$ PGE2, PGI2 and NO levels $\rightarrow$ inhibits afferent arteriolar vasodilation $\rightarrow$ $\downarrow$ GFR (and RBF)
 - (c) Long term $\rightarrow$ $\downarrow$ renin release $\rightarrow$ $\downarrow$ AII-induced efferent arteriolar vasoconstriction $\rightarrow$ $\downarrow$ GFR (and RBF)
 - (ii) $\downarrow [NaCl]$ or GFR causes the macula densa to:
 - (a) Initially release Nitrous Oxide $\rightarrow$ causes immediate afferent arteriolar vasodilation $\rightarrow$ $\uparrow$ GFR (and RBF)
 - (b) Delayed release of PGE2/PGI2 $\rightarrow$ causes (i) afferent arteriolar dilation, and (ii) renin release from JG cells $\rightarrow$ AII-induced efferent arteriolar constriction $\rightarrow$ $\uparrow$ GFR (and RBF)

(2) Extrinsic control of RBF:

- (a) Circulating hormones:
 - Afferent arterioles:
 - Dilation → PGE-2, PGI-2, DA, ANP, NO, kinins → ↑ RBF
 - Constriction → High dose AII, NAd, ET-1, Adenosine, ADH → ↓ RBF
 - Efferent arterioles:
 - Dilation → Inhibition of AII → ↑ RBF
 - Constriction → Low dose AII → ↓ RBF
- (b) Renal SNS (noradrenergic) nerves have a minor role:
 - (i) Constricts BOTH afferent and efferent arterioles → ↓ RBF
 - (ii) Stimulates renin secretion (via β_1 receptors on JG cells) → ↑ AII production
→ afferent and efferent arteriolar vasoconstriction → ↓ RBF

(e) *To describe the hepatic and splanchnic circulation.*

Hepatic blood flow → 1.5 L/min (30% of C.O.) or 60 mL/100g/min at rest → the liver receives blood supply (and oxygenation) from BOTH:

- (1) Hepatic artery:
 - Derived from abdominal aorta via coeliac artery (hepatic branch)
 - Supplies liver with (i) 30% of total HBF (300-500 mL/min), and (ii) 40-50% total hepatic O₂ supply (well-oxygenated blood; SaO₂ → 98%)
 - Characterised by → High pressure (90-100 mmHg), high flow velocity (16-18 cm/s), and high-resistance arteriolar system (such that arteriolar pressure ↓ to 35 mmHg)
 - Blood flow autoregulated → dependent on metabolic demand post-prandially
- (2) Hepatic portal vein:
 - Drains blood from GI tract (Eg. intestines, stomach, pancreas, gallbladder) and spleen → contains digestive products (GIT), and waste products of RBC destruction (spleen)
 - Supplies liver with (i) 70% of total HBF (1000-1200 mL/min), and (ii) 50-60% total hepatic O₂ supply (poorly oxygenated blood; SvO₂ 50-85%)

Aside:

- Fasting → SvO₂ ~85% (↑↑ than MVB due to ↑ mesenteric arterial shunting through the intestinal capillaries, which drain into portal veins)
- Post-prandially → SvO₂ ↓ to ~ 50%

- Characterised by → Low pressure (5-10 mmHg), low flow velocity (9 cm/s), low resistance portal venous system (5-10% of that in hepatic artery), and VALVELESS venous system
- Blood flow NOT autoregulated → dependent on blood flow to GIT/spleen

Hepatic O₂ consumption and extraction:

- “Hepatic O₂ consumption” is 50 mL O₂/min (20% of body’s O₂ consumption) or 2 mL/100g/min at rest
- “Hepatic O₂ extraction” is very efficient (cf. other organs) → this is important b/c O₂ consumption can be maintained with ↓ total HBF by ↑↑↑ O₂ extraction at sinusoids!

Aside: With acute haemorrhage → ↓ O₂ supply due to (i) ↓ total HBF (↓ PV > HA) and (ii) mobilisation of 50% sinusoidal blood reserve into systemic circulation → BUT O₂ delivery maintained due to ↑↑↑ sinusoidal O₂ extraction

Control of hepatic blood flow:

$$\text{Hepatic arterial blood flow} = \frac{\text{MAP} - \text{Hepatic venous pressure (HVP)}}{\text{Hepatic vascular resistance (HVR)}}$$

$$\text{Portal venous blood flow} = \frac{\text{Portal venous pressure} - \text{HVP}}{\text{HVR}}$$

Thus → factors that influence (i) MAP, (ii) PVP, (iii) HVP, and (iv) HVR control HBF!

Intrinsic regulation of HBF:

- (i) Hepatic artery is autoregulated
 - ↓ hepatic arterial pressure → hepatic arterial blood flow is maintained by ↓ hepatic artery resistance (UNTIL P_{SYSTOLIC} < 80 mmHg)
 - ↑ hepatic arterial pressure → flow maintained due to ↑ hepatic artery resistance
- (ii) Portal vein is NOT autoregulated

- Portal vein flow is LINEARLY related to portal venous pressure (I.e. $\uparrow$ portal venous pressure = $\uparrow$ portal venous flow)

Note: "Hepatic arterial buffer response" exists $\rightarrow$ semi-reciprocal interrelationship between HA and PV blood flow based upon the autoregulatory nature of these vessels:

- (i) Δ PV blood flow $\rightarrow$ causes a compensatory Δ HA blood flow (as HA is autoregulated) $\rightarrow$ maintains HBF:
 - $\downarrow$ PV blood flow $\rightarrow$ compensatory $\uparrow$ HA blood flow 2° $\downarrow$ HA resistance (due to vasodilation triggered by build-up of adenosine metabolite)
 - $\uparrow$ PV blood flow $\rightarrow$ compensatory $\downarrow$ HA blood flow 2° $\uparrow$ HA resistance (due to reflex vasoconstriction triggered by a myogenic mechanism)
- (ii) Δ HA blood flow does NOT cause a compensatory Δ in PV blood flow (as PV is NOT autoregulated) $\rightarrow$ thus HBF cannot be maintained

Extrinsic control of HBF:

- (1) Neuroendocrine factors:
 - Catecholamines:
 - NAd/Adr – (i) PV constriction (α), (ii) HA constriction initially (α) $\rightarrow$ dilation later on (β), and (iii) HV constriction (α) $\rightarrow$ generally cause $\uparrow$ HVR $\rightarrow$ $\downarrow$ HBF
 - Dopamine – Minimal effects at physiological conditions

Hepatic artery has $\rightarrow$ (i) α -receptors, (ii) β -receptors, and (iii) DA receptors
 Portal vein has $\rightarrow$ (i) α -receptors, and (ii) DA receptors
 Hepatic vein has $\rightarrow$ α -receptors

- AII – HA, PV and HV constriction $\rightarrow$ $\uparrow$ HVR $\rightarrow$ $\downarrow$ HBF
- ADH – Only PV constriction $\rightarrow$ $\uparrow$ HVR $\rightarrow$ $\downarrow$ HBF
- Glucagon – Both HA and PV dilation $\rightarrow$ $\downarrow$ HVR $\rightarrow$ $\uparrow$ HBF
- VIP/Secretion – Dilate HA only $\rightarrow$ $\downarrow$ HVR $\rightarrow$ $\uparrow$ HBF
- (2) External factors:
 - Physiological:
 - Δ MAP/C.O. – $\uparrow$ MAP/C.O. $\rightarrow$ $\uparrow$ HBF; $\downarrow$ MAP/C.O. $\rightarrow$ $\downarrow$ HBF
 - Spontaneous breathing – $\uparrow$ hepatic venous outflow with inspiration ($\uparrow$ HBF), and $\downarrow$ with expiration ($\downarrow$ HBF)
 - Exercise – $\downarrow$ HBF due to splanchnic vasoconstriction ($\uparrow$ HVR)
 - Feeding – $\uparrow$ HBF due to increased intestinal blood flow ($\uparrow$ PVP)
 - PaCO_2 – $\downarrow$ PaCO_2 causes $\downarrow$ HBF due to $\downarrow$ PV blood flow (PV constriction and $\uparrow$ HVR); opposite with $\uparrow$ PaCO_2
 - PaO_2 – $\uparrow$ PaO_2 has little effect on HBF; $\downarrow$ PaO_2 initially $\downarrow$ HA blood flow (but this normalizes in 30 mins) and has minimal effects on PV blood flow
 - Iatrogenic/pathophysiological:
 - MAP/C.O. – $\uparrow$ MAP/C.O. (Eg. inotropes) $\rightarrow$ $\uparrow$ HBF; $\downarrow$ MAP/C.O. (Eg. shock due to anaphylaxis, hypovolaemia, cardiogenic) $\rightarrow$ $\downarrow$ HBF
 - IPPV/PEEP – $\downarrow$ HBF due to a $\downarrow$ C.O./MAP and $\uparrow$ HVP
 - Surgical factors (Eg. laparoscopy, ligation, Etc.) $\rightarrow$ $\downarrow$ HBF due to external compression on vessels, SNS activation or local reflexes
 - Anaesthetic factors – $\downarrow$ HBF due to $\downarrow$ C.O./MAP and obtundation of "hepatic arterial buffer response"

Hepatic microvasculature:

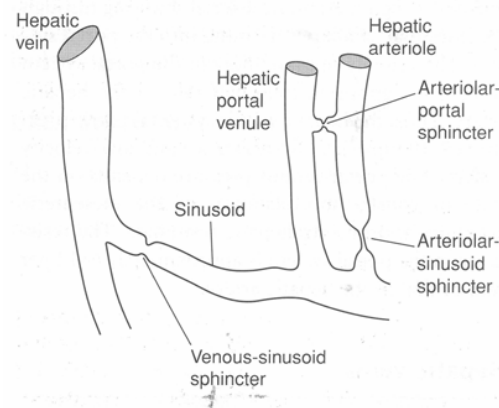
- "Sinusoids" are the low pressure microvascular capillary system of acinus $\rightarrow$ produced from anastomosis of hepatic arteriole and portal venule

- Role of sinusoids:
 - (i) Facilitates exchange of nutrients/waste between blood and hepatocytes
 - (ii) Act as a reservoir for blood

Aside:

- Hepatic sinusoids and portal venous system are very compliant → can normally store 500 mL of blood (10% BV)
- With hypervolaemia → additional 1000 mL can be stored (total 1500 mL) → due to ↑↑ compliance (or distensibility) of the system at higher venous pressures
- With hypovolaemia → 350 mL of stored blood can be returned to circulation → due to (i) relaxation of hepatic venule sphincters (allows portal blood to bypass sinusoids → directly enters hepatic vein), and (ii) mobilisation of sinusoidal blood in response to systemic catecholamines

- It is a low pressure system (2 mmHg) → due to high resistance pre-sinusoidal sphincters (esp arteriolar-sinusoid and arteriolar-portal sphincters)
- Blood within these sinusoids flow from the periphery of the acinus (where “portal triad” lies) → into central vein → then into hepatic vein → then leaves liver into IVC
- There are three sets of sphincters implicated in the sinusoidal system:
 - (i) Arteriolar-Portal sphincter (between the hepatic arteriole and portal venule)
 - (ii) Arteriolar-Sinusoid sphincter (between the hepatic arteriole and sinusoid)
 - (iii) Venous-Sinusoid sphincter (between the sinusoid and hepatic vein)



(f) *To describe the skin circulation.*

Skin consists of a network of capillaries, arterioles, arteriovenous anastomoses, and venules (venous capacitance system of 1.5 L blood) → receives 500 mL/min (10% of C.O.) or 13 mL/100g/min at rest

Main function of cutaneous blood flow is “thermoregulation” → skin blood flow can ↑ by 30x to promote heat loss during heat-stress, and ↓ by 10x to prevent heat loss during cold-stress

Note – Secondary function of skin blood flow is maintaining systemic arterial BP via “arterial BRR” → skin blood flow can ↓ by 10x with arterial hypotension, thereby preserving blood flow to brain and heart

Skin blood flow is controlled by SNS input from the hypothalamic “thermoregulatory centre”:

- (1) Directly controlled by “SNS vasomotor nerve” stimulation of α 1-mediated vascular SM contraction (Ie. ↑ SNS outflow → ↑ α 1-mediated arteriolar SM tone and vasoconstriction → ↓ blood flow)
- (2) Indirectly controlled by “SNS cholinergic nerve” stimulation of sweat glands (Ie. ↑ SNS cholinergic nerve outflow causes bradykinin release from sweat glands → dilates skin arterioles and ↑ blood flow)

Important to note – Skin blood flow is NOT autoregulated → however, initial ↓ skin blood flow 2° to SNS-mediated vasoconstriction can be overcome by local metabolic factors with prolonged cold-stress, which cause vasodilation and ↑ skin blood flow

Skin circulation is effective in thermoregulation b/c it acts like a “radiator”:

- (1) Vasoactive control of arterioles and arteriovenous shunts in ears, nose, lips, hands/feet
 - Vasodilation occurs due to (i) direct effects of heat, (ii) ↓ α -mediated vasoconstriction a/w ↓ SNS outflow, and (iii) ↑ bradykinin release from sweat glands a/w ↑ SNS cholinergic outflow → causes ↑ cutaneous blood flow (by up to 30x) and ↑ heat loss during heat-stress
 - Vasoconstriction occurs due to (i) direct effects of cold, (ii) ↑ α -mediated vasoconstriction a/w ↑ SNS outflow, and (iii) ↓ bradykinin release from sweat glands a/w ↓ SNS cholinergic outflow → causes ↓ cutaneous blood flow (by up to 10x) and ↓ heat loss during cold-stress
- (2) Counter-current system of cutaneous arteries and veins within the limbs permit direct heat exchange b/t them (Ie. cold blood returning from deep veins of a limb acquire heat from the arterial system → minimises heat loss to the environment)

(g) *To describe muscle (skeletal) circulation.*

Skeletal muscle blood flow → 1200 mL/min (20%) or 3 mL/100 g/min at rest

Note – Skeletal muscle blood flow can ↑ to 20x with exercise to 20 L/min

Factors that affect skeletal muscle blood flow:

- (1) Local metabolic control (“autoregulation”)
 - ↑ muscle activity is a/w ↑ metabolism → produces local metabolites (K^+ , ADP, H^+ , CO_2 , temperature, Etc.) and ↓ pO_2 → causes arteriole SM to relax and ↓ arteriolar tone → results in vasodilation and ↓ arteriolar resistance → ↑ blood flow
- (2) Extrinsic SNS control:
 - (i) Basal SNS outflow from medullary vasomotor centre at rest produces significant α -mediated skeletal muscle arteriolar tone (and vasoconstriction) → b/c of the large bulk of body muscle mass, skeletal muscle arteriolar tone represent a significant % of SVR that can be altered by arterial BRR (Ie. by ↑ or ↓ basal SNS outflow) to control systemic arterial BP

Note – With severe ↓ BP (Ie. haemorrhage) → arterial BRR ↑ basal SNS outflow to cause arteriolar vasoconstriction → ↓ skeletal muscle perfusion to 20% of normal!

- (ii) “Sympathetic cholinergic vasodilator” nerve activity ↑ with exercise and defence response → causes ↓ skeletal muscle arteriolar tone and ↑ blood flow
 - (iii) Circulating Adr from adrenal medulla → cause β_2 -mediated vasodilation (and ↑ blood flow) at low [], but α_1 -mediated vasoconstriction (and ↓ blood flow) at ↑ []
- (3) Extrinsic muscle compression:
 - During muscle contraction, ↑ intramuscular pressure impedes muscle blood flow → this is important as there are two types of exercise:
 - (a) Isotonic (dynamic) exercise – Usual form of exercise where muscle length changes → muscle blood flow occurs during relaxation b/t muscle contraction
 - (b) Isometric (static) exercise – Muscle length remains constant → continuous muscle contraction causes significant ↓ muscle blood flow

Important to note – Effect of muscle activity plays on muscle blood flow plays a vital role in the “Skeletal muscle pump” → ↑ muscle activity (Ie. exercise) promotes venous return back to the heart, as veins compress and expel blood during muscle contraction, and dilate and fill with blood during muscle relaxation. Of note, venous valves ensure unidirectional flow of blood

(h) *To describe utero-placental circulation.*

(I) Uteroplacental blood flow:

- At term → uteroplacental BF is 500-700 mL/min (10% maternal C.O.) at rest of which:
 - (i) 70-90% of this BF enters the intervillous space (via the spiral arteries) → NOT autoregulated as blood flow is “pressure-dependent” (see factors below)
 - (ii) 10-30% of this BF supplies the myometrium/deciduas (via the basal arteries) → autoregulated blood flow
- Blood flow to the intervillous space (which participates in substance exchange with foetal blood) is affected by the following factors:

$$UBF = \frac{UAP - UVP}{UVR}$$

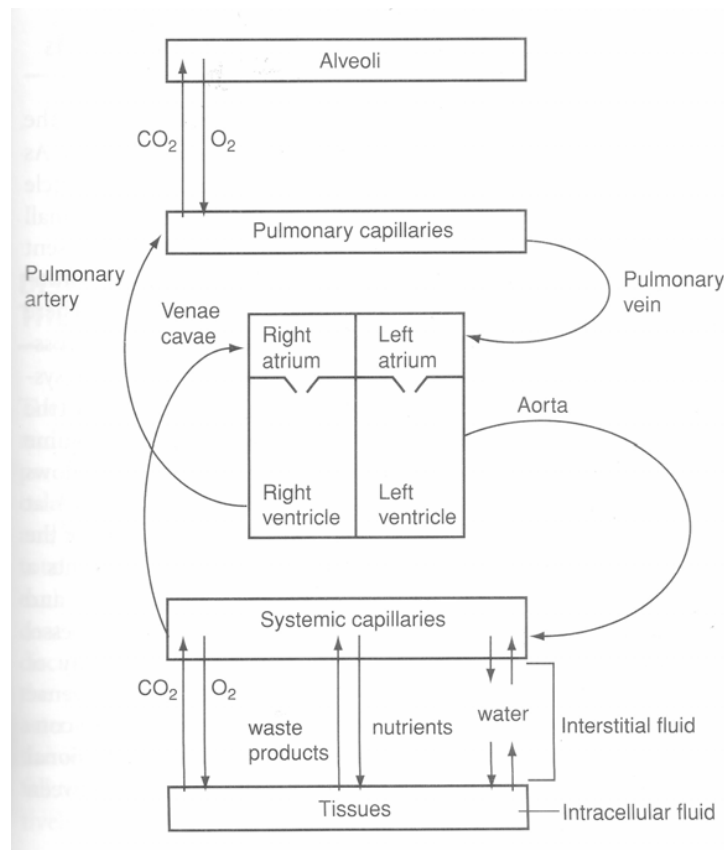
- (1) Uterine arterial pressure (UAP):
 - Maternal arterial BP → ↓ MABP (Ie. due to SNS block 2° neuraxial block, hypovolaemia, supine hypotension syndrome, Etc.) causes ↓ UAP → ↓ UBF
- (2) Uterine venous pressure (UVP):
 - Uterine tone and contractions → ↑ tone/contractions (Ie. due to contractions, oxytoxics, ketamine, Etc.) causes ↑ UVP → ↓ UBF
- (3) Uterine vascular resistance (UVR):
 - Uterine arteriolar tone → ↑ vasoconstriction (Ie. a/w essential HT and PET, α-adrenoceptor stimulation (by endogenous SNS innervation, catecholamines or sympathomimetics), and vasopressin) causes ↑ UVR → ↓ UBF

(II) Umbilical blood flow:

- At term → umbilical BF is 360 mL/min (25-50% of foetal C.O. (≈ 1000 mL/min))
- It is “autoregulated” (cf. uterine BF) → involves vasodilators (PCI-2/NO) derived from vascular endothelium
- BF is ↓ with severe hypoxia, ↑ BGL, catecholamine and cord compression

I. STRUCTURE AND FUNCTION OF THE HEART

To describe the structure and functional significance of the conductive, excitatory and contractile elements of the heart.



Structure and function of the cardiovascular system (CVS):

The CVS consists of two circulatory systems that function in series, each with its own functions:

- (1) Pulmonary circulation (low pressure system) – RV pumps blood through pulmonary capillaries → assists in transfer of O_2 and CO_2 between blood and air in lungs
- (2) Systemic circulation (high pressure system) – LV pumps blood through systemic capillaries → assists in exchange of O_2/CO_2 , metabolic nutrients, waste products, H_2O between blood and peripheral tissues

Important to note – Systemic circulation is vital in peripheral organ function also:

- (i) GIT → nutrient absorption and liver function
- (ii) Renal → H_2O /electrolyte homeostasis and excretion of waste products
- (iii) Endocrine → secrete hormones (Eg. ANP) and circulate others
- (iv) Immune role → transport of Ab and immune cells
- (v) Thermoregulation → regulate skin blood flow and heat loss
- (vi) Skeletal muscle → body movement
- (vii) Distribution of TBW b/t intra- and extra-vascular spaces

Structure of the systemic circulation → see notes on “Cardiovascular Physiology – The peripheral vascular system”)

Structure of the pulmonary circulation → see notes on “Respiratory Physiology – Pulmonary circulation”

Functional anatomy of the heart:

The heart is a muscular pump with 4 chambers – (i) RA, (ii) RV, (iii) LA, (iv) LV

The right side of the heart (RA and RV) and left side of the heart (LA and LV) pump blood around the pulmonary and systemic circulations, respectively, in series → both sides lack direct connections with each other and are separated by the pulmonary and systemic circulations

Walls of the cardiac chambers are made of 3 layers:

- (i) Endocardium → endothelial surface lining inside of chambers
- (ii) Myocardium → cardiac muscle layer

Aside – Cardiac muscle cells:

- Similar striations as skeletal muscle cells → made up of sarcomeres (Z-Z lines) containing myosin thick filaments (A band) and thin actin filaments (I band) attached to Z lines
- Cardiac muscle cells are shorter and thicker (cf. skeletal muscle cells) and form branching networks with “Intercalated discs” at ends of adjacent fibres that form low-resistance “Gap junctions” → causes cardiac muscle cells to act as a “functional syncytium”

- (iii) Epicardium → mesothelial layer lining the outside of chambers

Note – Chamber pressures influence the thickness of the cardiac chamber walls → atria have thin walls (as they operate at low pressures), while the ventricles – esp the LV – have thicker walls (as they operate at higher pressures)

A fibrous pericardium encloses the entire heart → pericardial fluid lubricates the small pericardial space between the pericardium and the heart

The heart contains valves (whose movements are passive) to ensure unidirectional blood flow within the cardiac chambers:

- (i) Atrioventricular valves (tricuspid and mitral valves)
 - o Located b/t atria and ventricle → prevent reflux of blood into atria during ventricular contraction
 - o Chordae tendineae connect these valves to papillary muscles within ventricles → limit eversion or bulging of AV valves into atria during ventricular contractions
- (ii) Semi-lunar valves (aortic and pulmonic valves)
 - o Located b/t ventricles and outgoing artery (aorta or pulmonary artery) → prevent reflux of blood into ventricles during ventricular relaxation

Electrical circuitry of the heart (see notes on “Cardiovascular physiology – Electrical properties of the heart”) → consists of:

- (i) SA node
- (ii) Atrial pathways
- (iii) AV node (which is surrounded by a fibrous atrioventricular ring separating and preventing direct electrical coupling of atria and ventricles)
- (iv) Bundle of His and Purkinje fibres

Coronary vasculature → see notes on “Cardiovascular physiology – Regional circulation”

Heart has dual ANS nerve supply → both of which originate from “medullary vasomotor centre”:

- (i) PNS
 - o Cardiac PNS fibres are sent along two sets of vagus nerves (CN X) → right vagus nerve (slows depolarisation of SAN) and left vagus nerve (slows conduction through AVN)

- ACh is released by these fibres → ↓ HR

Note – Effect of ACh is rapid BUT brief due to ↑ [AChE] in synapses

- (ii) SNS

- Cardiac SNS fibres originate from intermediolateral columns of T1-T4 of spinal cord → synapse in middle or stellate ganglia → then complex nerve plexus to heart
- NAd is released by these fibres → ↑ HR and myocardial contractility

Note – Effect of NAd is slow BUT of longer duration

IV. THE PERIPHERAL VASCULAR SYSTEM

- (a) *To describe the distribution of blood volume and flow in the various regional circulations and to explain the factors that may result in redistribution of blood.*
- (b) *To explain the factors that determine systemic blood pressure and its regulation.*
- (c) *To describe total peripheral vascular resistance and factors that affect it.*
- (d) *To describe the mechanisms involved in local vascular control and autoregulation.*
- (e) *To describe the mechanisms involved in maintaining blood flow to individual organs in the presence of changed perfusion pressure (autoregulation).*
- (f) *To describe the essential features of the micro-circulation including fluid exchange (Starling forces) and control mechanisms present in the pre- and post-capillary sphincters.*

(I) Overview of Systemic Circulation:

Role of systemic circulation:

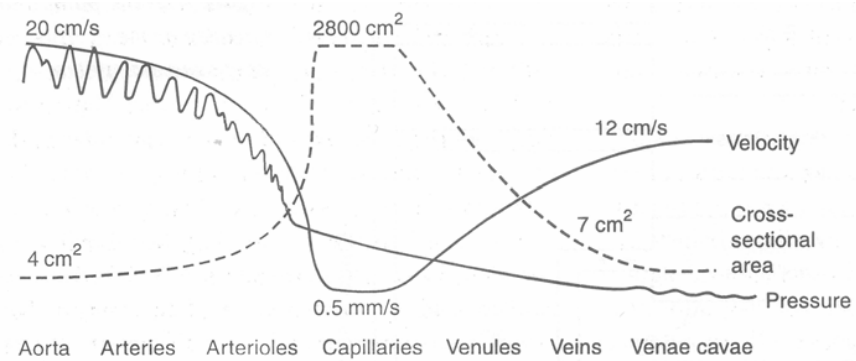
- Closed-circuit circulatory system with a pump-oxygenator designed for distribution (I.e. bulk transport of nutrients, waste, other substances) and exchange

Components of systemic circulation:

- (1) Left ventricular → pumps blood around the systemic circulation
- (2) Aorta and large (elastic and muscular) arteries → low-volume and high-pressure vessels that:
 - (i) Act as a low-resistance conduit that rapidly distributes blood ejected from LV into the peripheral circulation, then into various organs of the body
 - (ii) Act as an “auxiliary pump” during diastole to convert intermittent LV output into a continuous (but pulsatile) flow of blood in the peripheral circulation (as per “Windkessel effect”)
- (3) Arterioles (“resistance vessels”) → vessels with strong muscular walls that:
 - (i) Determines distribution of C.O. to organs by their variable vascular resistance → vital in “autoregulation” of organ blood flow
 - (ii) Influences TPR → one of the key determinant of arterial BP
 - (iii) Reduces intravascular pressure → promotes continuous flow of blood in capillary system downstream
- (4) Capillaries → thin-walled vessels lined with a single layer of endothelial cells on a basement membrane that:
 - (i) Exchanges H_2O /electrolytes, gases, nutrients and wastes b/t blood and tissues
 - (ii) Controls distribution of fluid b/t intra- and extravascular compartments
- (5) Venous system (“capacitance vessels”) → high-volume and low-pressure vessels that:
 - (i) Act as a low-resistance conduit for the return of blood from peripheral circulation back to the heart
 - (ii) Acts as a “blood reservoir” that can buffer the effects of acute Δ s in BV (ie. can constrict and ↑ effective BV with hypovolaemia, and accommodate heaps of blood (due to its high compliance) and ↓ effective BV with hypervolaemia)
- (6) Lymphatics (see “Fluids and Electrolytes Physiology”)

Cross-sectional area, pressure and blood flow velocities within the systemic circulation:

	Cross-sectional area	Mean pressure	Blood flow velocity	Important points
Aorta and arterial system (arteries and arterioles)	Aorta = 4 cm^2 → CSA ↑ along arterial system (esp arterioles)	Aorta = 100 mmHg → pressures ↓ along arterial system (esp arterioles)	Aorta = 20 cm/s → velocity ↓ along arterial system (esp arterioles)	Small arteries and arterioles have ↑↑↑ SVR → causes high pressure generated by LV to ↓ significantly, and dampens pulsatile arterial blood flow into a continuous one
Capillaries	Very large (2800 cm^2) – despite 25% being patent only at rest	Arterial end = 35 mmHg Venous end = 15 mmHg	Very slow (0.5 mm/sec)	Large CSA and slow, continuous blood flow → favours diffusion of nutrients and waste products b/t blood and tissues
Venous system (venules, veins, venae cavae)	CSA ↑ along venous system → veins = 7 cm^2	Venule = 10-15 mmHg Veins = 4-8 mmHg Vena cava = 0-2 mmHg	Velocity ↑ along venous system → venae cavae = 12 cm/s	



Composition of vessel walls and vessel size:

Important to note – Vessel walls (apart of capillaries) have 3 layers:

- (1) Intima → sheet of endothelial cells
- (2) Media → smooth muscle cells embedded in matrix of elastin and collagen
- (3) Adventitia → inelastic CT sheath

- (1) Aorta and arteries – Large diameter with thick walls (elastic tissues⁺⁺⁺, CT⁺⁺⁺, SM⁺⁺) → low-resistance conducting vessels that stretch in systole and conduct blood flow during diastole by elastic recoil
- (2) Arterioles – Smaller diameter and wall thickness cf. aorta/arteries (SM⁺⁺⁺⁺, elastic tissues⁺⁺, CT⁺⁺) → high-resistance vessels that can vary vascular resistance and control organ blood flow
- (3) Capillaries – Very small diameter and thin-walled (only has endothelial lining – no SM, CT or elastic tissues) → ideal for exchange of gases, fluid, nutrients, waste b/t tissue and capillary blood
- (4) Venule, veins and venae cavae – Progressively larger diameter and wall thickness (elastic tissue⁺⁺, SM⁺⁺, CT⁺⁺⁺) → low-resistance capacitance vessels that can stretch and accommodate large volumes of blood

Aside – “Endothelium”:

The entire CVS (heart and blood vessels) is lined with a single layer of endothelial cells which forms the surface that contacts blood

Endothelium plays major roles:

- (1) Capillary function → exchange of nutrient, gases, fluid and waste products between tissue and blood
- (2) Autoregulation of blood flow → produces several “vasoactive substances” (Eg. prostacyclin, NO, endothelins)
- (2) Coagulation and fibrinolysis → intact endothelium prevents exposure of collagen and tissue factor in subendothelial matrix, and also produces various factors (Eg. tissue factor, thrombomodulin, tPA, heparan sulphate)
- (3) Angiogenesis → produces several growth factors (Eg. VEGF)

Important to note – There are several vasoactive substances released by the endothelium

- Role – These substances are vital in local metabolic “autoregulation” of peripheral blood flow → they act locally on arteriolar smooth muscle tone (in a paracrine manner) to alter the calibre of the supplying arteriole → produce matching of regional blood supply with the metabolic demands of the tissue
- Endothelial vasoactive substances include:

- (1) Prostacyclin
 - Produced in endothelium from arachidonic acid by prostacyclin synthase in the constitutive COX-1 pathway
 - Effect – (i) Inhibits platelet adhesion and aggregation (main role) and (ii) Promotes blood flow by causing arteriolar vasodilation (activates adenylyl cycles, which $\uparrow$ cAMP and $\downarrow$ MLCK activity, thus leading to $\downarrow$ arteriolar smooth muscle tone)
 - Triggers – Shear stress caused by pulsatile flow
- (2) Nitric oxide (EDRF)
 - Synthesised in endothelium by NO synthetase-3 from Arginine, O_2 and NADPH
 - Effect – When released from endothelial cells, it diffuses into VSMC $\rightarrow$ activates soluble guanylyl cyclase to produce cGMP, which stimulates myosin phosphatase $\rightarrow$ triggers smooth muscle relaxation and arteriolar vasodilation $\rightarrow$ $\uparrow$ blood flow
 - Trigger – Released from endothelial cells in response to shear stress, various neurotransmitters (ACh, substance P, VIP, bradykinin, histamine), and products of tissue metabolism (hypoxia, hypercarbia, acidosis, temperature, lactic acid, K^+)
- (3) Endothelins
 - There are three types:
 - ET-1 – Potent vasoconstrictor found in endothelium, brain and kidney
 - ET-2 (GIT) and ET-3 (adrenal) are less important
 - Effect – Act on ET-A receptors (GPCR) on vascular SM $\rightarrow$ stimulates phospholipase C and causes arteriolar vasoconstriction $\rightarrow$ $\downarrow$ blood flow
 - Trigger – Synthesised in endothelium (but not stored) in response to endothelial damage, AII, catecholamines, hypoxia, insulin, thrombin. Inhibited by NO, ANP, PCI-2

(II) Blood Volume and Its Distribution:

“Total blood volume” → 5 L (in 70 kg adult) or 70 mL/kg (in adults and newborns > 12 months)

Note – Total blood volume is ↑ in newborn < 12 months → 80-100 mL/kg

Distribution of blood volume in body:

Supine:

Systemic circulation	75 %
- (i) Veins	55 %
- (ii) Arteries	13 %
- (iii) Arterioles	2 %
- (iv) Capillaries	5 %
Central blood volume	25 %
- (i) Heart	8 %
- (ii) Pulmonary circulation	16 %

Standing:

Systemic circulation	85 %
- (i) Veins	65 %
- (ii) Arteries	13 %
- (iii) Arterioles	2 %
- (iv) Capillaries	5 %
Central blood volume	15 %
- (i) Heart	6 %
- (ii) Pulmonary circulation	9 %

Important to note – When going supine to standing, distribution of blood volume changes in both the:

- (i) Systemic circulation (↑ from 75% to 85%) → BV in veins ↑ from 55% to 65%
- (ii) Central blood volume (↓ from 25% to 15%) → BV in heart ↓ from 8% to 6%, and BV in pulmonary circulation ↓ from 16% to 9%

Remember – “Pulmonary circulation” has 450 mL of BV → 3% in capillaries (70 mL), 8% in arteries, and 5% in veins

Blood reservoir:

- Whole venous system acts as a “blood reservoir” because of its high-capacitance, BUT some organ veins hold a very large amount of blood → especially the lungs (100-200 mL), liver (500 mL) and skin (several 100’s of mLs)

Others: Large veins in limbs (esp with muscle activity or postural change)
 Spleen (< 100 mL)
 Splanchnic circulation (300 mL)

- These blood reservoirs are important during hypovolaemia or haemorrhage (esp BV loss > 20% or > 1 L) → where SNS-mediated venoconstriction under arterial BRR control causes these reservoirs to return blood back into the systemic circulation → ↑ “effective” blood volume → ↑ VR back to heart to maintain C.O. and arterial BP

(III) Systemic Circulation: Aorta and Large Arteries

Overview of aorta and large arteries:

- “Low-volume” and “high-pressure” vessels → comprise 13% of total BV (650 mL) and have a MAP of 100 mmHg (with SBP 120 mmHg and DBP 80 mmHg)
- Large diameter with thick walls → consists of elastic tissues⁺⁺⁺, CT⁺⁺⁺, SM⁺⁺
- Aorta has CSA = 4 cm² and blood flow velocity is 20 cm/s

Function of aorta and large arteries:

Function of aorta and large (elastic) arteries:

- (1) Low resistance conduit that rapidly distributes blood ejected from LV into the peripheral circulation
- (2) Act as “auxiliary” pump in series with the LV during diastole that converts intermittent LV output into a continuous (albeit pulsatile) blood flow in the peripheral circulation → see “Windkessel effect” below

Note – LV has intermittent blood flow as pressure goes from 120 mmHg during systole (I.e. flow occurs) to 0 mmHg during diastole (I.e. flow ceases) → BUT aortic blood flow is continuous as pressures fluctuate b/t 120 mmHg during systole and 80 mmHg during diastole due to the “Windkessel effect” (see below)

“Windkessel effect”:

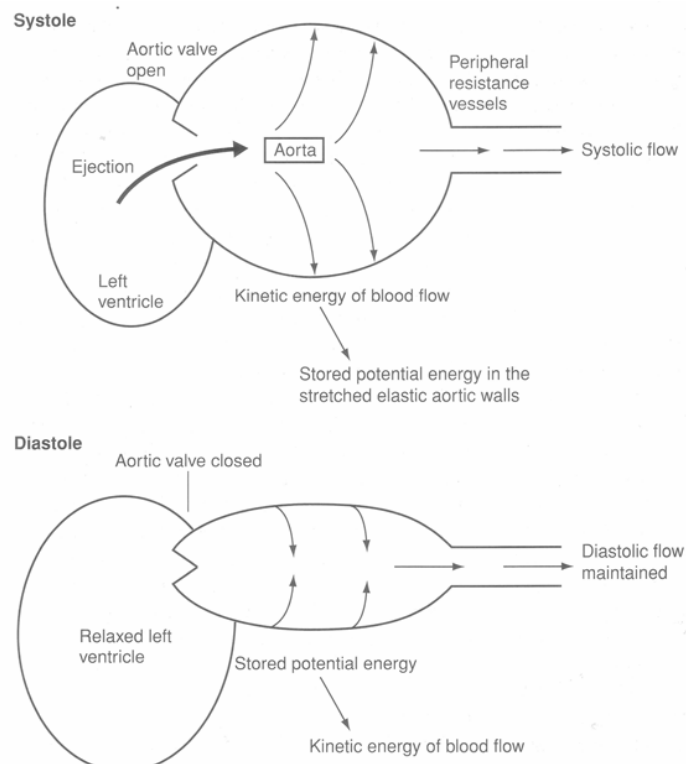
This effect has two important roles:

- (1) Convert intermittent LV output into continuous blood flow in peripheral circulation
- (2) ↓ cardiac workload (I.e. ↓ work is needed for LV to generate intermittent blood flow cf. continuous flow)

The effect is dependent on 3 factors:

- (1) Elasticity of aorta and large arteries
- (2) Presence of resistance in peripheral vessels
- (3) Presence of a functioning aortic valve to prevent retrograde flow into LV

Mechanism:



- During ventricular systole, SV of blood is ejected into the elastic aorta and large elastic arteries at an arterial pressure (SBP) of 120 mmHg → but due to the impedance to flow by arteriolar peripheral resistance, only a small amount (33%) of blood reaches peripheral tissues and a larger amount (66%) of blood remains within the aorta and large elastic arteries → this distends their elastic walls, causing kinetic energy of blood flow to be stored in the stretched aortic/arterial walls as potential energy
- During ventricular diastole, aortic valve closes (and prevents back flow into LV) and the stretched aortic/arterial wall contracts → causes stored potential energy to be converted back into kinetic energy → generates an arterial pressure (DBP) of 80 mmHg → restores blood flow (albeit in pulsatile manner)

Note – “Windkessel effect” is ineffective (I.e. ↓ continuous peripheral blood flow) with:

- (1) ↓ elasticity of aorta and large arteries (I.e. ageing) → aorta/arteries are unable to store/release energy as effectively → less constant peripheral blood flow
- (2) ↓ peripheral resistance (I.e. use of peripheral vasodilators) → ↓ TPR and ↓ amount of blood stored in aorta and large arteries at end-systole → less constant peripheral blood flow
- (3) Presence of incompetent AV (I.e. AR) → ↑ backflow into LV and ↓ amount of blood stored in aorta and large arteries at end-systole → less constant peripheral blood flow

Function of large (muscular) arteries:

- Low-resistance conduit that rapidly distributes C.O. in peripheral circulation to all organs of the body

Arteries and Arterial Blood Pressure:

“Blood pressure” → force exerted by blood against any unit area of the vessel wall (such that a BP of “x” mmHg means the force exerted in blood can elevate column of Hg against gravity to “x” mm)

Note:

- (1) “Mean arterial pressure” (MAP) → average arterial pressure acting during the cardiac cycle → it is determined by either:
 - (i) Averaging the pressure under an “arterial pressure vs time” curve (I.e. AUC divided by time)
 - (ii) Using known SBP and DBP

$$\text{MAP} = \text{DBP} + 1/3 (\text{SBP} - \text{DBP})$$

- (2) “Systolic blood pressure” (SBP) → maximal arterial pressure achieved during systolic phase of cardiac cycle
- (3) “Diastolic blood pressure” (DBP) → lowest arterial pressure achieved during diastolic phase of cardiac cycle
- (4) “Pulse pressure” (PP) → difference between SBP and DBP

$$\text{PP} = \text{SBP} - \text{DBP}$$

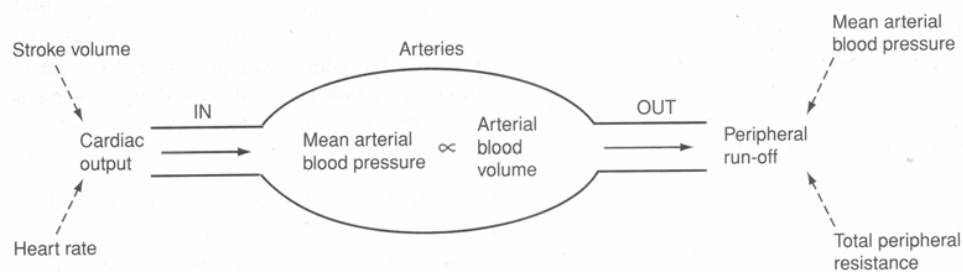
Determinants of MAP:

Main determinants of MAP – (i) CO and (ii) TPR – alter MAP by changing arterial blood volume:

$$\text{MAP} = \text{CO} \times \text{TPR}$$

Rationale – MAP is determined by the amount of blood volume in the arterial system at any one time → this depends on:

- (i) Amount of blood entering the aorta as “C.O.” → C.O. is determined by HR and SV
- (ii) Amount of blood leaving the arteries as peripheral run-off (PRO) into capillaries → PRO is determined by the TPR of arterioles (whereby $\uparrow$ TPR = $\downarrow$ PRO, and vice versa)



Note:

- MAP is stable when C.O. and PRO are equal
- If $PRO > C.O.$ (I.e. $\downarrow$ TPR or $\downarrow$ C.O.) → then $\downarrow$ arterial BV → $\downarrow$ MAP
- If $C.O. > PRO$ (I.e. $\uparrow$ C.O. or $\uparrow$ TPR) → then $\uparrow$ arterial BV → $\uparrow$ MAP

Important to note – Arterial wall compliance is NOT a determinant of MAP, BUT it does determine the RATE at which a new MAP is attained upon Δ in C.O. and TPR! (Eg. $\downarrow$ compliant vessel (I.e. in elderly) → have more rapid Δ in MAP with Δ s in TPR or C.O.)

Determinants of arterial pulse pressure:

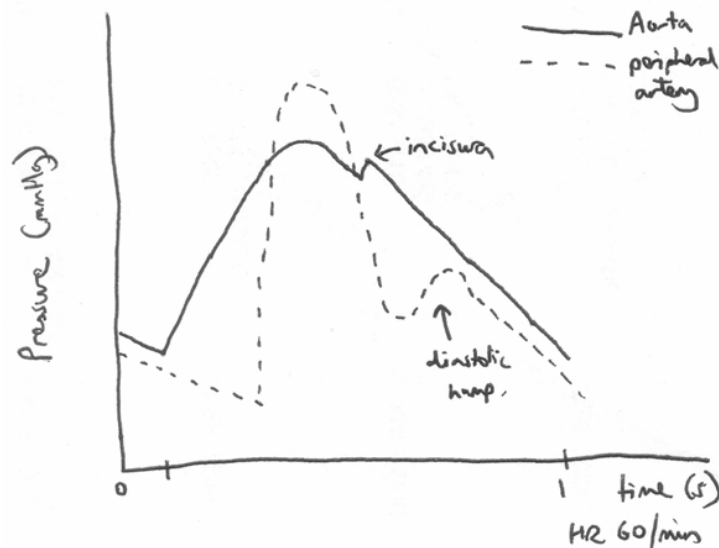
- (1) Stroke volume
 - During systole, arterial pressure $\uparrow$ from DBP 80 to 120 mmHg SBP b/c of $\uparrow$ arterial BV produced by rapid LV ejection of a stroke volume's content of blood → produces PP of 40
 - If SV is $\uparrow$ → both SBP and DBP $\uparrow$, BUT $\uparrow$ DBP is less → thus, PP $\uparrow$
- (2) Arterial compliance
 - $\downarrow$ arterial compliance (Eg. elderly) → $\uparrow$ PP b/c (i) LV ejection of blood into stiff arteries produces $\uparrow$ rise in SBP for the same SV ejected into arterial system, and (ii) Windkessel effect (which normally maintains DBP) is impaired by $\downarrow$ arterial elasticity, resulting in $\downarrow$ DBP

Arterial pulse contours:

Systolic stretching of aortic wall during ventricular ejection initiates a pressure wave that travels peripherally along the aortic and arterial wall → these pressure waves travel much faster (m/s) than blood flow (cm/sec) → thus, pulses palpated over peripheral arteries is due to transmission of pressure waves transmitted peripherally (rather than actual blood flow in the peripheral artery)

Significance: (i) Presence of a peripheral arterial pressure wave means that the heart is pumping (I.e. mechanical activity is present)
(ii) Peripheral arterial pressure waves can be recorded even if there is total distal occlusion of the peripheral artery and no blood flow

Arterial pressure waveform changes as blood flows away from the aorta and through the arterial tree → these changes are the result of damping, reflection, resonance, and changes in velocity transmission of different pressure components (I.e. high pressure components travel faster)



Aortic root pressure waveform:

- ↑ aortic pressure upon opening of aortic valve (and ejection of blood into aorta) during systole phase of cardiac cycle → peak pressure 120 mmHg reached
- “Incisura” present after closure of aortic valve → due to retrograde flow in proximal aorta against closed aortic valve
- Aortic pressure gradually ↓ to a trough pressure of 80 mmHg during diastolic phase of cardiac cycle → due to “Windkessel effect” (I.e. elastic potential energy of blood stretching the aorta during systole is converted back into kinetic energy of blood flow during diastole)

Peripheral arterial waveform (Eg. radial artery), in comparison to aortic root pressure waveform has:

- Delayed onset → due to travel distance
- Steeper upstroke and downstroke → due to ↓ vessel compliance
- Narrowed systolic wave (I.e. shorter duration waveform) → due to ↓ vessel compliance, which ↑ velocity 2° to ↑ peak pressures
- Elevated systolic wave (and ↑ SBP) → due to reflection and resonance (I.e. summation of waveforms) 2° to ↓ vessel compliance
- ↓ DBP → due to loss of “Windkessel effect” 2° to ↓ vessel compliance
- ↓ PP (but MAP is unchanged) → due to ↑ SBP and ↓ DBP
- High frequency components (esp Incisura) disappear → due to damping
- Diastolic hump (or dicrotic wave) appears during diastole → due to reflection and resonance

Important to note – Effect on arterial pressure waveform in the peripheries vary with age:

- In the young → changes in pressure waveform are more marked
- In the elderly → changes in pressure waveform are less marked (I.e. resemble aortic pressure waveform) → this is b/c of (i) ↓ compliant arteries (I.e. stiffened arterial system) and (ii) ↓ myocardial contractility → causes slower upstroke, higher systolic peak, and less delayed onset (as pressure waves travel faster in less compliant and pressurised aorta)

(IV) Systemic Circulation: Arterioles

Overview of arterioles:

- High-resistance vessels characterised as being “low-volume” and “high-pressure” → comprise 2% of total BV (100 mL) and have a MAP of 100 mmHg (with ↑ SBP and ↓ DBP cf. aorta and large arteries due to ↓ vessel compliance (Ie. ↑ damping, ↑ resonance and reflection))
- Smaller diameter and wall thickness cf. aorta/arteries (SM⁺⁺⁺⁺, elastic tissues⁺⁺, CT⁺⁺)

Function of arterioles:

- (1) Influences TPR → b/c arterioles are the main site of resistance to blood flow in the CVS, and resistance can vary in response to several factors (see below)
- (2) Influences arterial BP → b/c TPR is one of the main determinants of arterial BP

For example:

- Arteriolar vasoconstriction (Ie. due to ↑ SNS outflow) → ↑ TPR → ↑ MAP
- Arteriolar vasodilation (Ie. due to ↓ SNS outflow) → ↓ TPR → ↓ MAP

- (3) Determines distribution of C.O. (or blood flow) to organs by altering the vascular resistance of the organ → vital in “autoregulation” of organ blood flow (Ie. matching of local blood flow to the organ’s requirements for its function)

Important to note – Organ blood flow is determined by – (i) perfusion pressure to organ, and (ii) resistance of its vascular bed:

$$\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$$

$$\text{Organ blood flow} = \frac{\text{Mean arterial pressure}}{\text{Organ vascular resistance}}$$

As all systemic vascular beds are exposed to the same perfusion pressure (or MAP), the distribution of C.O. to each individual organ is thus determined by the state of vascular SM tone in its supplying arteriolar (resistance) vessels (or organ vascular resistance)

- (4) ↓ intravascular pressure and converts pulsatile arterial blood flow (at mean pressure 100 mmHg) into a steady blood flow (at 35 mmHg) → promotes continuous blood flow in capillary system downstream
- (5) Influences distribution of total body H₂O b/c intravascular and interstitial fluid compartments at tissue capillary beds → b/c degree of arteriolar vasoconstriction alters the hydrostatic pressure drop across the arterioles → this affects capillary P_{HYDROSTATIC}, which influences bulk flow of fluid b/t these compartments

For example:

- Arteriolar vasoconstriction (and ↑ resistance) → ↑ hydrostatic pressure drop → ↓ capillary P_{HYDROSTATIC} → net bulk flow of fluid from ISF into capillaries
- Arteriolar vasodilation (and ↓ resistance) → ↓ hydrostatic pressure drop → ↑ capillary P_{HYDROSTATIC} → net bulk flow of fluid from capillaries into ISF

Determinants of arteriolar resistance (and total peripheral resistance):

Assuming “laminar” blood flow → then arteriolar resistance to blood flow obeys “Hagen-Poiseuille’s equation”:

$$R = \frac{8nl}{\pi r^4}$$

n = viscosity
l = length
r = radius

- (1) Radius of arteriolar vessel (r) → MAIN determinant of arteriolar resistance b/c (i) it can change markedly by several factors (see below), and (ii) it affects resistance inversely to the 4th power

- $\uparrow$ vessel radius (I.e. vasodilation) $\rightarrow$ causes $\downarrow$ resistance
- $\downarrow$ vessel radius (I.e. vasoconstriction) $\rightarrow$ causes $\uparrow$ resistance

Important to note – Tonic SNS nerve output to arterioles and spontaneous contractile (myogenic) activity of arteriolar SM $\rightarrow$ resting state of partial vasoconstriction

Factors that control of arteriolar SM tone and vessel radius:

- Local factors:
 - o (a) Local myogenic control (aka. “pressure autoregulation”)
 - Organ blood flow (mainly brain and kidneys) is kept constant over a wide range of arterial BP $\rightarrow$ this is caused by compensatory changes in the organ’s arteriolar resistance in response to changes in arterial BP within that range
 - Mechanism – $\uparrow$ arterial BP causes $\uparrow$ arteriolar wall stretching $\rightarrow$ arteriolar SM respond by contracting and $\uparrow$ arteriolar tone $\rightarrow$ this results in vasoconstriction and $\uparrow$ arteriolar resistance $\rightarrow$ offsets $\uparrow$ local blood flow a/w $\uparrow$ arterial BP (the opposite outcome occurs with $\downarrow$ arterial BP)
 - o (b) Local metabolic control (aka. “metabolic autoregulation”)
 - Organ blood flow (mainly brain, heart and skeletal muscle) is varied in accordance to the metabolic needs of the organ
 - Mechanism – $\uparrow$ organ metabolic activity leads to $\uparrow$ local production of a “mediator” ($p\text{CO}_2$, H^+ , K^+ , adenosine, P_i , lactic acid, pyruvate, NO , temperature) and $\downarrow$ $p\text{O}_2$ $\rightarrow$ causes arteriole SM to relax and $\downarrow$ arteriolar tone $\rightarrow$ results in vasodilation and $\downarrow$ arteriolar resistance $\rightarrow$ $\uparrow$ organ blood flow
 - o (c) Local tissue pressure control
 - Organ blood flow (mainly in kidneys) is affected by extravascular compression by ISF
 - Mechanism – $\uparrow$ organ blood flow produces $\uparrow$ ISF that compresses the arterioles from the outside $\rightarrow$ generates $\uparrow$ arteriolar resistance that limits blood flow
 - o (d) Local tissue vasoactive chemical control
 - (i) Glandular cells (esp salivary, sweat and intestinal glands) produce kallikrein when “active” $\rightarrow$ converts inactive kininogens to active kinins (esp bradykinin) that relaxes arteriolar SM and $\downarrow$ arteriolar tone $\rightarrow$ vasodilation and $\uparrow$ blood flow
 - (ii) Endothelial cells produce vasoactive substances – PGI_2 and NO are vasodilators, while ET-1 is a vasoconstrictor
 - (iii) Activated platelets produce TXA_2 , which causes vasoconstriction
- Systemic factors:
 - o (a) Extrinsic SNS control
 - Arterioles in skin, kidneys and GIT have profuse SNS supply $\rightarrow$ NAd from nerve endings act on α_1 -adrenoceptors to cause vasoconstriction (and β_2 -adrenoceptors to cause vasodilation – but effect is weaker!)
 - Due to the tonic SNS outflow from medullary vasomotor centres, arterioles have a basal level of vasoconstriction $\rightarrow$ the degree of basal vasoconstriction (and arteriolar resistance) can be varied by altering SNS outflow
 - Of note, skeletal muscle has “SNS cholinergic vasodilator” supply under cortical control $\rightarrow$ causes vasodilation with exercise to $\uparrow$ skeletal muscle blood flow
 - o (b) Extrinsic PNS control
 - PNS control of arterioles is less important $\rightarrow$ vessels of external genitalia have dual ANS supply with PNS dilator nerves and SNS constrictor supply; PNS activation in heart, brain and lungs have an uncertain role
 - o (c) Extrinsic hormonal control
 - (i) Adrenaline (from adrenal medulla) $\rightarrow$ effect on organ blood flow depends on the relative % of α_1 - and β_2 -adrenoceptors in the arteriole
 - (ii) Ang II (from RAAS) $\rightarrow$ vasoconstriction (via AT_2R)
 - (iii) ADH (from posterior pituitary) $\rightarrow$ vasoconstriction (via V_1R)
 - (iv) ANP (from RA) $\rightarrow$ vasodilation (via ANPR)

- (2) Viscosity of blood (η) $\rightarrow$ less important determinant of arteriolar resistance
- $\uparrow$ blood viscosity (Eg. polycythaemia, hyperproteinaemia, Etc.) $\rightarrow$ causes $\uparrow$ resistance
 - $\downarrow$ blood viscosity (Eg. isovolaemic haemodilution, anaemia, Etc.) $\rightarrow$ causes $\downarrow$ resistance
- (3) Length of arteriolar vessel (l) $\rightarrow$ NOT a factor in determining resistance as it is fixed

(V) Systemic Circulation: Microcirculation

“Microcirculation” → refers to the collection of the smallest blood vessels in the body, which includes small arterioles, metarterioles, pre-capillary sphincters, capillaries and small venules

Capillary and the microcirculation:

- Capillaries arise directly from either (i) arterioles or (ii) metarterioles (which are SM-containing vessels that connect arterioles and venules) → SM-based “pre-capillary sphincter” exists at the origin of these capillaries

Note – Some tissue microcirculation contain “arterio-venous shunts” under ANS control (Eg. skin) → do not partake in normal microcirculatory functions (Ie. AV shunts in skin have a role in thermoregulation)

- Blood flow in these capillaries is “intermittent” → b/c capillary blood flow is dependent on the patency of the supplying arteriole/metarteriole and the pre-capillary sphincter, intermittent contraction and relaxation of SM of arterioles/metarterioles and pre-capillary sphincters in response to local tissue metabolic factors leads to “intermittent” blood flow (Ie. $\downarrow$ pO₂ causes SM relaxation and $\uparrow$ blood flow)
- Capillary microcirculation has a very large cross-sectional area (2800 cm²) → this is vital for capillary function (esp nutrient and metabolite exchange) BUT produces slow blood flow velocities (0.5 mm/sec) → it takes 2 secs for RBC to traverse capillary vessel at rest
- In most tissues, only 25% of capillaries are open at rest → closed capillaries form a “reserve capacity” of blood flow that can open up quickly in response to $\uparrow$ tissue metabolic activity when additional blood flow and $\downarrow$ diffusion distance is required
- Capillary vessel density in tissues is variable → $\uparrow$ capillary density in metabolic organs (Eg. heart, skeletal muscle), but $\downarrow$ density in inactive tissues (Eg. cartilage)
- Systemic capillaries contain 5% of total BV (250 mL) and pulmonary capillaries contain 3% of total BV (70 mL)

Aside – Structure of capillaries:

- Thin-walled vessels lined with a single layer of endothelial cells on a basement membrane
- Their walls have narrow intercellular clefts b/t adjacent endothelial cells with varying permeability → its permeability is $\uparrow$ in certain organs (esp liver) and in venous ends of tissues (cf. arterial ends) due to wider and $\uparrow$ porous clefts, but $\downarrow$ in brain (Ie. BBB) due to presence of “tight junctions”
- Narrow with a diameter of 5-10 μ m → this means RBC (7 μ m wide) need to deform and flex to pass through the capillary system
- Thin wall (only 0.5 μ m thick) → short diffusion distance b/t blood and tissue

Important to note – Despite the thin capillary wall, the capillary can withstand high hydrostatic pressures (up to 35 mmHg) due to its small radius → due to “Law of LaPlace” where:

$$\text{Wall tension} = (\text{Pressure}) \times (\text{Radius})$$

So wall tension required to cause capillary rupture is kept low b/c of the small capillary radius, even at high intravascular pressures!

Functions of the capillaries and microcirculation:

The capillaries and microcirculation have two key functions:

- (1) Exchange of H₂O/electrolytes, gases, nutrients and wastes b/t blood and tissues
- (2) Control distribution of fluid b/t intra- and extravascular compartments

Movement of substances (Eg. fluids, nutrients, gases, Etc.) is important in the function of capillaries and the microcirculation → substances traverse across the capillary membrane via:

(1) Diffusion

- Most substances (EXCEPT large substances, such as albumin/proteins) traverse the capillary wall b/t blood and ISF via diffusion → obeys “Fick’s Law of Diffusion”, whereby rate of diffusion is proportional to [] gradient, surface area, solubility, and the inverse of diffusion distance and MWT
- “Lipid-soluble” substances (including O₂ and CO₂) diffuse across the capillary wall through the thin walls of the capillary endothelial cells, while “water-soluble” substances (Eg. H₂O, electrolytes, glucose, urea, Etc.) diffuse through the capillary wall via the intercellular clefts b/t capillary endothelial cells

Note – Size of intercellular clefts influences the capillary permeability, and hence the ability of certain substances to diffuse across the capillary membrane (Ie. BBB in brain have tight junctions and no intercellular clefts → not even “water-soluble” substances can diffuse readily; hepatic sinusoids have large clefts → even large proteins can readily diffuse across)

(2) Filtration (or bulk flow)

- Capillary membrane is a semi-permeable membrane that is permeable to water and solute only (BUT impermeable to larger proteins (esp albumin)) → so a protein-free “ultrafiltrate” of plasma is filtered by bulk flow through the capillary wall by opposing hydrostatic and oncotic pressure (aka. “Starling forces”)
- Net fluid movement across the capillary wall is determined by “Starling’s Equation”:

$$\text{Bulk flow across capillary wall} = (K) \times (\text{NFP})$$

(i) “*Filtration coefficient*” (K) is determined by:

- (a) Area of capillary walls where transfer occurs
- (b) Permeability of capillary wall to H₂O (or “hydraulic conductivity”)

$$K = (\text{Area}) \times (\text{Hydraulic conductivity})$$

Example – Glomerular capillaries have ↑ K due to its ↑ “hydraulic conductivity”, and thus have ↑ net filtration (or bulk flow) of fluid

(ii) “*Net filtration pressure*” (NFP) is determined by the balance of opposing “Starling forces” across the capillary membrane, and the “Reflection coefficient”:

$$\text{NFP} = (P_C - P_{\text{ISF}}) - \sigma(\pi_C - \pi_{\text{ISF}})$$

Where:

- (a) P_C → capillary hydrostatic pressure
- (b) P_{ISF} → ISF hydrostatic pressure
- (c) π_C → capillary oncotic pressure
- (d) π_{ISF} → ISF oncotic pressure
- (e) σ (or “Reflection coefficient”) → permeability of capillary wall to proteins (Ie. ↓ σ in liver where capillary wall is permeable to proteins; ↑ σ in glomerulus where capillary wall is impermeable to proteins)

Important to note:

- Of the “Starling forces”, only capillary hydrostatic pressure (P_C) is under immediate physiological control, and thus an important influence in net fluid movement across capillary wall → factors that influence P_C are:
 - (i) Resistance of arterioles (“precapillary resistance”)
 - (ii) Resistance of venules/veins (“postcapillary resistance”)

$$\text{Capillary hydrostatic pressure (P}_C\text{)} \propto \frac{\text{Post-capillary resistance}}{\text{Pre-capillary resistance}}$$

For example:

- $\uparrow P_C$ occurs with either $\uparrow$ post-capillary resistance or $\downarrow$ pre-capillary resistance
 - $\downarrow P_C$ occurs with either $\downarrow$ post-capillary resistance or $\uparrow$ pre-capillary resistance
-
- Pre- and post-capillary resistances are controlled by the same local and systemic factors (see “factors that control arteriolar SM tone” above)
 - Of note, capillary hydrostatic pressure is also affected by arterial and venous BP $\rightarrow$ BUT venous BP have a greater effect (cf. arterial BP) b/c the $\uparrow$ resistance of arterioles dampen the effect of Δ s in BP on P_C

(3) Pinocytosis

- Large substances (Eg. protein, albumin) are taken across capillary wall by endo- and exocytosis through the capillary endothelial cell

In summary – Most substances move across capillary membrane by “diffusion” and “filtration”:

- (1) Diffusion
 - o Important for net movement of gases, nutrients, wastes across capillary wall
 - o Not important for net movement of H_2O across capillary wall $\rightarrow$ b/c no net osmotic gradient exists across the capillary wall, thus there is no net H_2O movement. However, volume of H_2O diffusion across capillary wall is large (300 mL H_2O per 100 mL tissues each minute), and can occur bidirectionally at any point along the capillary
- (2) Filtration
 - o Important for net movement of H_2O across capillary wall $\rightarrow$ b/c there is net movement of H_2O is determined by the imbalance of “Starling forces” across the capillary wall. However, volume of H_2O filtered is very small (1 mL H_2O per 100 mL tissue each minute), and occurs unidirectionally at any point along the length of the capillary only (Ie. either inward movement (absorption) or outward movement (filtration) at any given point and time)
 - o Not important for net movement of gases, nutrients, wastes (cf. diffusion)

Specific tissue microcirculation:

(1) Microcirculatory system of most tissues (esp skeletal muscle capillary):

There is net fluid loss from filtration of 2 mL/min or up to 4 L/day (as 20 mL/min of fluid are filtered but only 18 mL/min of fluid is later reabsorbed) $\rightarrow$ this means up to 4 L/day of fluid are returned back to the circulation by the lymphatic system

This is b/c of the following factors that influence “Starling’s equation”:

	Arteriolar end	Venous end	Comments
P_C	35 mmHg	15 mmHg	Main force driving fluid into ISF from vessel $\rightarrow$ it $\downarrow$ as blood flows from arterial to venous side
P_{ISF}	0 mmHg	0 mmHg	Negligible
π_C	28 mmHg	28 mmHg	Main force driving fluid from ISF into vessel $\rightarrow$ created by plasma albumin, which cannot cross capillary wall
π_{ISF}	3 mmHg	3 mmHg	Small amount of protein in ISF drives fluid into ISF from

			vessel
σ	~ 1	~ 1	Capillary wall is not permeable to proteins
NFP	+10 mmHg	-10 mmHg	At arterial end of capillary $\rightarrow$ bulk flow is out of vessel into ISF (net filtration) At venous end of capillary $\rightarrow$ bulk flow is into vessel from ISF (net absorption)

(2) Glomerulus:

There is net ultrafiltration of fluid in the glomerulus of 180 L/day (= GFR) into Bowman's capsule

This is b/c of the following factors that influence "Starling's equation":

	Arteriolar end	Venous end	Comments
P_{GC}	60 mmHg	58 mmHg	P_{GC} is high and remain high along length of capillary (unlike most microcirculatory systems where $P_C \downarrow$ along the capillary length) $\rightarrow$ of note, P_{GC} is influenced by ratio of afferent and efferent renal arteriolar resistances
P_{BC}	15 mmHg	15 mmHg	Remains unchanged
π_{GC}	21 mmHg	33 mmHg	σ of 1 means glomerular capillaries are impermeable to proteins $\rightarrow$ so no protein is lost into Bowman's capsule (and $\pi_{BC} = 0$), and all protein remain in the glomerular capillaries such that $\pi_{GC} \uparrow$ along the capillary length as fluid is being filtered out
π_{BC}	0 mmHg	0 mmHg	
σ	1	1	
NFP	+ 24 mmHg	+ 10 mmHg	Throughout the glomerular capillary, there is net bulk flow of fluid into Bowman's capsule (esp at arteriolar end)
K	High		Glomerular capillaries are highly permeable to H_2O

(3) Pulmonary microcirculation:

Alveolar walls are very thin and are covered in a very dense network of thinned-wall pulmonary capillaries $\rightarrow$ provides efficient gas exchange

Normally, there is net filtration of fluid into the pulmonary interstitium (10-20 mL/hr) $\rightarrow$ this is b/c of the following factors that influence the "Starling equation":

	Arteriolar end	Venous end	Comments
P_C	13 mmHg	6 mmHg	- Pulmonary capillary $P_{HYDROSTATIC}$ are lower cf. systemic capillaries, but are sufficient to perfuse the apical areas in an erect lung - Due to gravity effects in an erect lung, the bases have a $\uparrow P_C$ cf. apex (by 23 mmHg) - P_C is heavily affected by Δs in LA and PA pressures b/c of low PVR $\rightarrow$ unable to buffer Δs in pressures
P_{ISF}	-2 to 0 mmHg		$P_{ISF} \approx$ alveolar pressures transmitted into pulmonary interstitium $\rightarrow$ -ve pressures favour flow of fluid from interstitium into pulmonary lymphatics
π_C	28 mmHg		Main force driving fluid from ISF into vessel $\rightarrow$ created by plasma albumin, which cannot cross capillary wall readily
π_{ISF}	17 mmHg		Protein in ISF drives fluid into ISF from vessel
σ	0.5		Proteins readily "leak" across thin pulmonary capillary wall
NFP	+7.5 mmHg	+0.5 mmHg	There is net bulk flow of fluid is out of vessel into ISF (net filtration) $\rightarrow$ esp at arteriolar end of capillary

The excess fluid in pulmonary interstitium moves into perivascular and peribronchial spaces towards the hilum (which has a more -ve P_{ISF}) $\rightarrow$ fluid is then promptly removed by the lymphatics at the same rate (10-20 mL/hr)

Important to note:

- “Interstitial oedema” occurs when excess filtered fluid accumulates in the pulmonary interstitium → when various “safety mechanisms” (see below) are exhausted, excess fluid then moves into the alveoli to cause “Pulmonary oedema”
- The “safety mechanisms” that prevent pulmonary oedema include:
 - (i) ↑ lymphatic flow → ↑ fluid filtration promotes ↑ lymph flow to remove excess fluid
 - (ii) Oncotic buffering mechanism → $\pi_{\text{ISF}} \downarrow$ with ↑ fluid filtration b/c of (i) ↓ albumin is lost into the interstitium, and (ii) ↑ lymph flow which drains albumin out of interstitium → leads to ↓ fluid filtration
 - (iii) ↑ interstitial compliance → large volume of fluid can accumulate in interstitium w/o much ↑ P_{ISF}
 - (iv) Surfactant

Microcirculation and Oedema:

“Interstitial oedema” → accumulation of ISF in abnormally large amounts

This can be caused by:

- (1) ↑ volume of fluid leaving capillaries and entering ISF compartment

Note – According to “Starling’s equation”, this can occur with:

- ↑ P_C (Eg. ↑ venous pressure or venous obstruction)
- ↓ P_{ISF}
- ↓ π_C (Eg. ↓ plasma [protein], such as cirrhosis)
- ↑ π_{ISF} (Eg. presence of osmotically active substance in ISF)
- ↓ σ (Eg. histamine release a/w AIR)
- ↑ K (Eg. inflammation)

- (2) ↓ lymphatic drainage (Eg. axillary LN clearance)
- (3) ↑ total ECFV (Eg. ↑ $\text{Na}^+/\text{H}_2\text{O}$ retention states, such as CCF or cirrhosis)

Interstitial oedema collects in dependent areas → b/c of hydrostatic effects of gravity

(VI) Systemic Circulation: Venous system

Overview of venous system:

- Venous system consists of – (i) Venules, (ii) Veins, (iii) Venae cavae → presence of one-way valves promote unidirectional blood flow back to the heart
- From venule to venae cavae → progressively larger diameter and ↑ wall thickness (elastic tissue⁺⁺, SM⁺⁺, CT⁺⁺⁺)
- High capacitance vessels characterised as being “high-volume” and “low-pressure” → comprise 60% of total BV (3000 mL) and mean pressures of 10-15 mmHg in venules, 4-8 mmHg in veins, and 0-2 mmHg in venae cavae
- Venae cavae blood flow is 12 cm/s

Function of venous system:

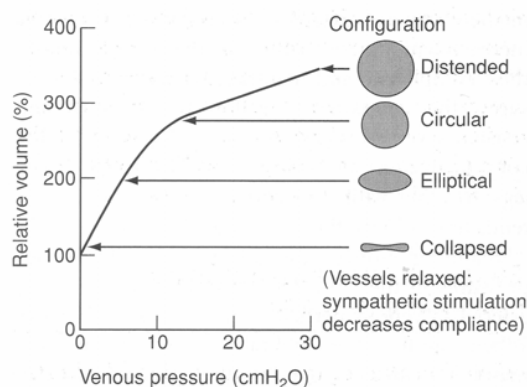
- (1) Low-resistance conduit for the return of blood from peripheral circulation back to the heart
- (2) Acts as a “blood reservoir” that can buffer the effects of acute Δ s in BV due to (i) its ↑ compliance (venous system is 25-30x more compliant cf. arterial system → veins have 4x capacity cf. arteries) and (ii) SNS innervation, which mediates the degree of venoconstriction

For instance:

- Hypervolaemia → high compliance of venous system allows 25-30x more BV to be stored per mmHg of pressure cf. arterial system, thus ↓ Δ s in effective BV
- Hypovolaemia → SNS-mediated venoconstriction pumps blood out venous system to ↓ Δ s in effective BV to maintain VR to heart and C.O.

Distensibility of veins:

- Shape of veins is altered by hydrostatic pressures within the vessel:



Note:

- Low venous pressures → vein collapses or becomes elliptical
- Moderate venous pressures → veins become circular with ↑ internal volume
- High venous pressure → veins become distended

- Consequences of changes in shape of veins:
 - (1) At low-moderate venous pressures (I.e. 0-10 cmH₂O when veins are elliptical or circular), veins are highly compliant and can accommodate large volumes of blood with only small changes in internal hydrostatic pressure
 - (2) At high venous pressures (I.e. > 10 cmH₂O when veins are distended), vein compliance ↓ as they are overstretched
 - (3) At low venous pressures, veins collapse and resistance to blood flow ↑
- Control of vein distensibility → venous wall SM is influenced by:
 - (1) SNS innervation – NAd stimulates α -adrenoceptor and causes venous SM contraction and ↑ tone → venoconstriction → ↑ venous pressures and ↓ venous compliance → moves blood out of venous system
 - (2) Humoral factors (Adr, AII, ADH) – Similar effect as NAd

Important to note – Basal SNS nerve outflow to veins causes tonic venous SM contraction (and “venomotor tone”) → BUT can be varied by “arterial BRR”