PRESENTING OUR

GKTEACH

STAGE 1 SERIES

MSA Education

~~FMS - CELL BIOLOGY AND SIGNALLING~~	~~MONDAY 13TH NOV 6PM~~
~~FMS - MOLECULAR AND CELL GENETICS~~	~~THURSDAY 16TH NOV 6PM~~
~~FMS - NUTRITION AND METABOLISM~~	~~TUESDAY 21ST NOV 6PM~~
~~ANATOMY OF RESPIRATORY AND CARDIOVASCULAR SYSTEMS~~	~~WEDNESDAY 29TH NOV 13:30PM~~
PHYSIOLOGY OF RESPIRATORY AND CARDIOVASCULAR SYSTEMS	WEDNESDAY 29TH NOV 4PM
FPP - PHARMACOLOGY	MONDAY 4TH DEC 6PM
RESPIRATORY PHYSIOLOGY	MONDAY 11TH DEC 6PM
RESPIRATORY ANATOMY	THURSDAY 14TH DEC 6PM

MAKE SURE TO COME ALONG!

Cardiovascular Physiology

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Learning Objectives

- To learn and understand the basics of cardiac conduction and rhythm
- To recap the stages of the cardiac cycle and why it is important
- To understand the basic principles of the body's intrinsic control of blood flow, pressure and cardiac output
- To recall the process of tissue fluid exchange
- To relate the concepts learnt to physiological mechanisms of adaptation

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Initiation of the Heartbeat

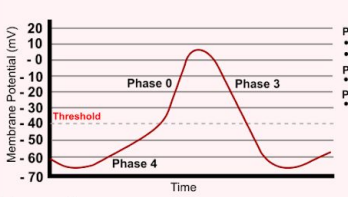
How are heart rhythms generated?

The heart myocardium has an intrinsic capacity to generate electrical potentials but it must be coordinated for any kind of effective contraction

The Sinu-Atrial Node is the primary pacemaker of the heart which generates 'heart beat' impulses at…

What does electrical activity in SAN look like?

Pacemaker Action Potential



Ion Channels

Phase 4
- HCN "Funny" Current (If)
- T-type Calcium Channels

Phase 0
- L-type Calcium Channels (Primarily)

Phase 3
- Voltage-gated Potassium Channels

Lineage ©

How is the heart rate kept at the correct rhythm?

The Cardiac Conduction System

But why is the heart rate variable if it is only dependent on the SAN?

Membrane Clock:
The If (funny current) channel which causes depolarisation when the SAN is hyperpolarised (paradoxical)

Ivabradine is a medication licensed to slow the heart rate used in heart failure which blocks the If channels

Calcium Clock:
Cyclical changes in calcium ions due to calcium transient in myocardial cells

Key Terms:
- Chronotropy:
- Inotropy:
- Lusitropy:

The Process
1. SAN generates impulse
2. Impulse spreads over atrial myocardium to AVN
3. There is a delay at the AVN to allow atrial filling before conduction
4. Impulse spreads to Bundle of His and splits into left and right branches
5. Conduction finishes with Purkinje fibres

Sympathetic:
- Noradrenergic transmission acts via B1 adrenoreceptors (Gs)
- This increases intracellular cAMP which phosphorylates cation channels and activates If via PKA
- Noradrenergic stimulation also increases inotropy

Parasympathetic:
- Cholinergic transmission via M2 channels (Gi/o)
- Decreases intracellular cAMP therefore changing ion currents and inhibiting if

The Heart is mainly under vagal tone at rest and sympathetic activation is normally in exercise or stress

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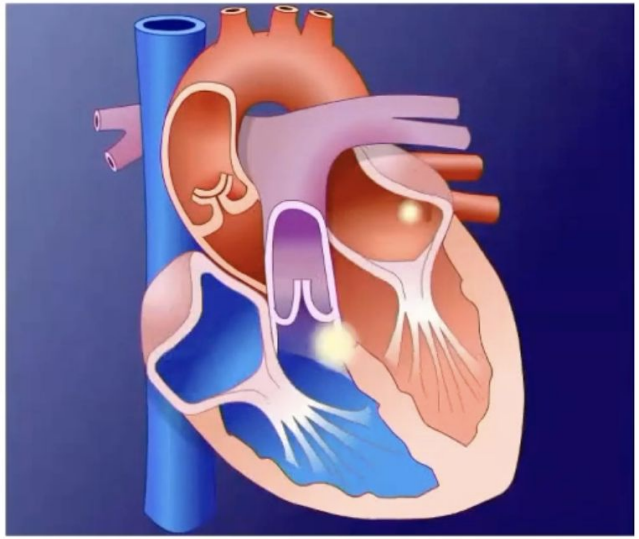
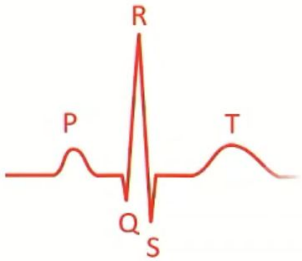
Reference electrode



V



P: Atrial depolarisation

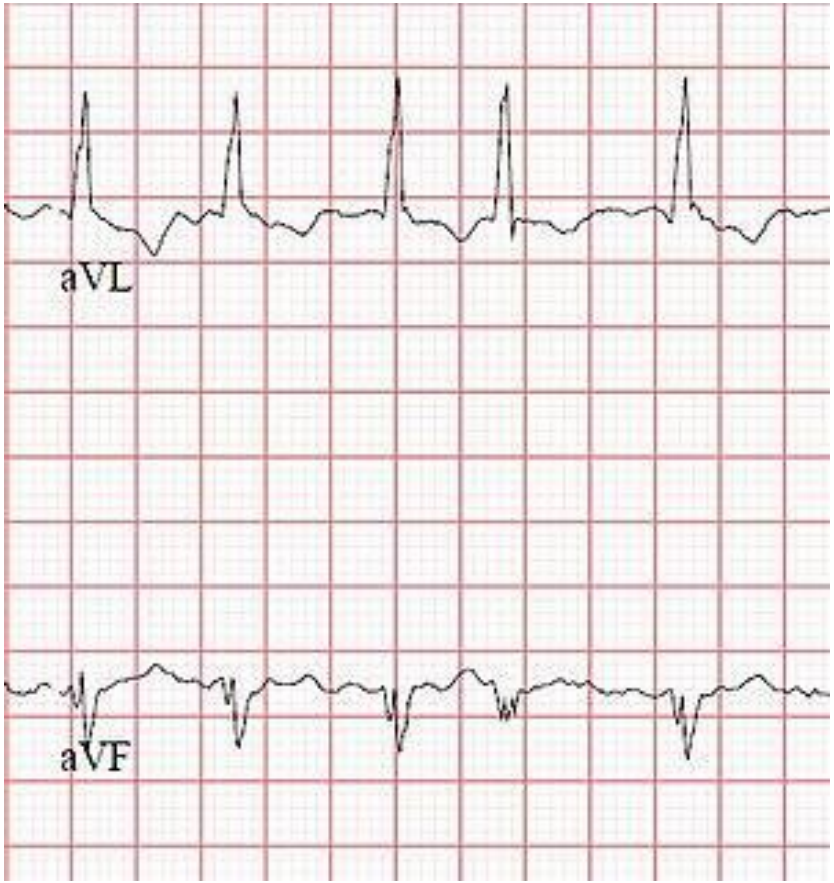
Q: Depolarisation of the septum (towards the atria)

R: Depolarisation of the ventricles (towards apex)

S: Depolarisation of the ventricles (towards atria)

T: Repolarisation of the ventricles (towards endocardium)

Recording electrode


aVL
aVF

The Cardiac Cycle

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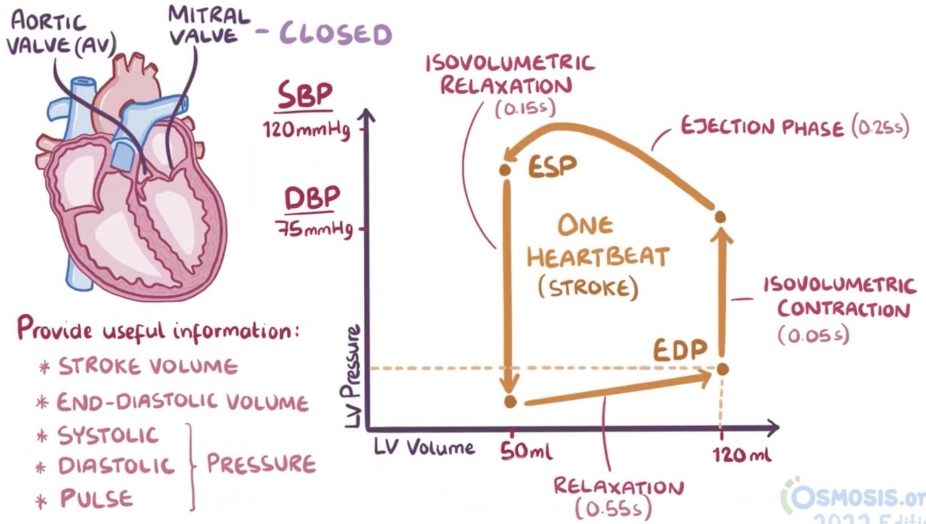
Pressure Changes in the Cardiac Cycle

- Healthy valves have very low resistance so open with little pressure difference

1. Ventricle at EDV
2. Mitral Valve Opens
3. Blood flows into LV
4. Atrial kick occurs as LA contracts
5. Mitral Valve Closes
6. Isovolumic contraction
7. Aortic Valve opens
8. Ejection of blood into aorta as LV contracts
9. Aortic Valve closes
10. Isovolumic relaxation

The dichotic notch is a bump on the aortic pressure when blood ejected from ventricle meets blood in aorta



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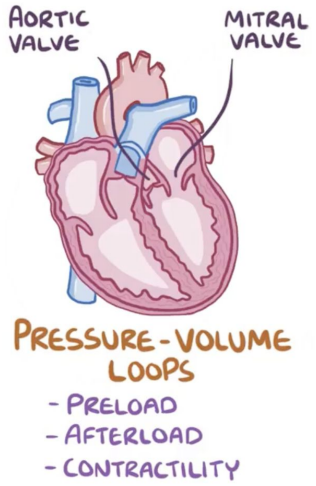
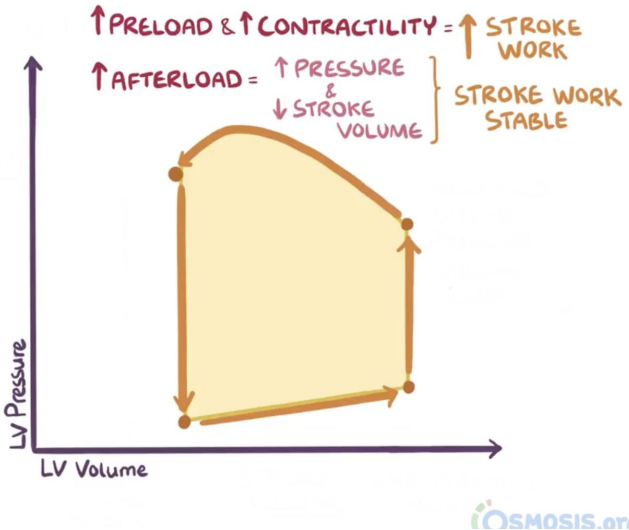
Pressure-Volume Loops

- Pressure volume loops measured using sensing catheters
- Shows changes in pressure and volume in LV
- Can calculated Stroke Volume, Stroke Work, Ejection Fraction, Systolic and Diastolic function
  - Stroke Volume = EDV-ESV
  - EF = SV/EDV x 100
  - Stroke volume is integrated area in loop
  - Ejection fraction measures how much blood is exerted from heart





$$EF(\%) = \frac{SV}{EDV} \times 100$$

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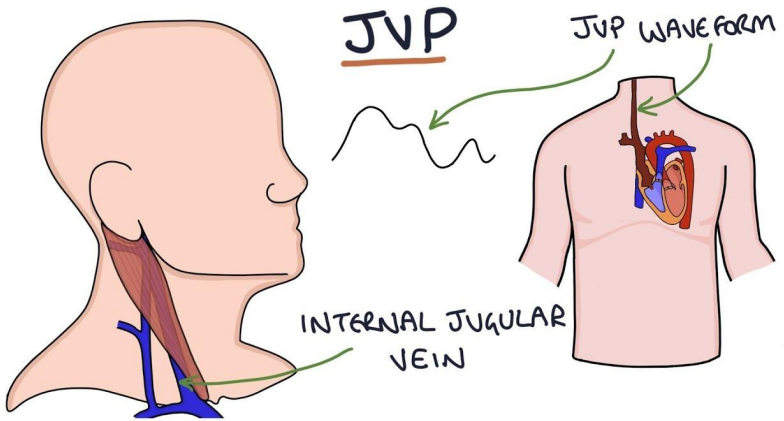
Jugular Venous Pulse

- Jugular Vein collapses 5cm above heart where venous pressure is 0mmHg
- No valves between Jugular Vein and Atria so direct pulse measurement
- JVP is a biphasic pulse between 0-8mmHg
    - a wave - Atrial contraction
    - c wave - Carotid pulse/Ventricular contraction
    - x wave - Atrial relaxation
    - v wave - Pressure rises from Venous return
    - y wave - Atrial emptying
- Internal jugular vein measured when patient at 45 angle 3cm above manubriosternal angle
    - External jugular is valvular, superficial and doesn't drain to SVC
- Tricuspid stenosis - a wave is enhanced
- Tricuspid regurgitation - v wave enhanced



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Arterial Pulse

- Arterial pulse changes as we move away from heart
- Arterial pulse is monophasic and differs based on essential artery measured
- Small bounce when aorta recoils from stored elastic potential energy - reflected wave
- Wave forms affected by damping, compliance, resonance and interference
- Effect of age, atherosclerosis and artery hardening on arterial pulse
    - Age, atherosclerosis and artery hardening alter composition and elasticity of wall so size of reflected wave decreases, as less recoil during diastole

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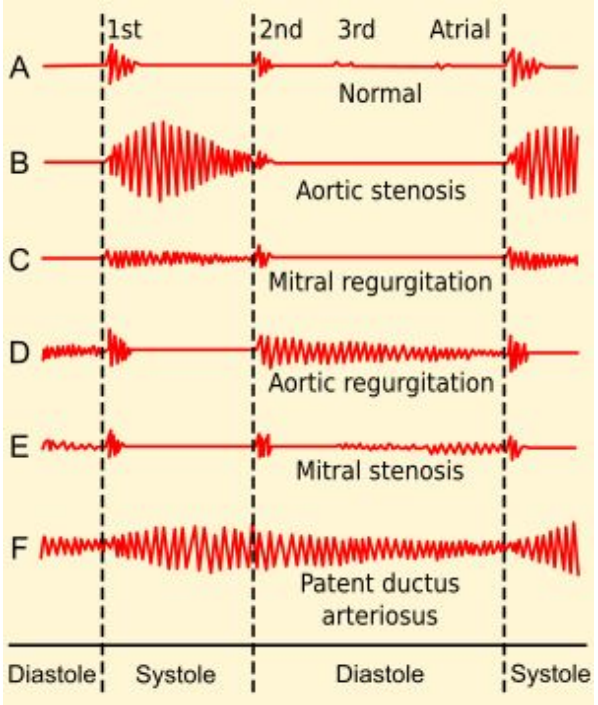
Heart Sounds

- S1 and S2 are primary heart sounds
- S3 and S4 are extra heart sounds heard during pathologies
    - S3 - Opening of AV valves and refilling
    - S4 - Atrial systole heard when EDP raised
- Heart murmurs are caused by valve pathologies
- Diastolic murmurs - Mitral Stenosis/Aortic Incompetence
- Systolic murmurs - Mitral Incompetence/ Aortic Stenosis



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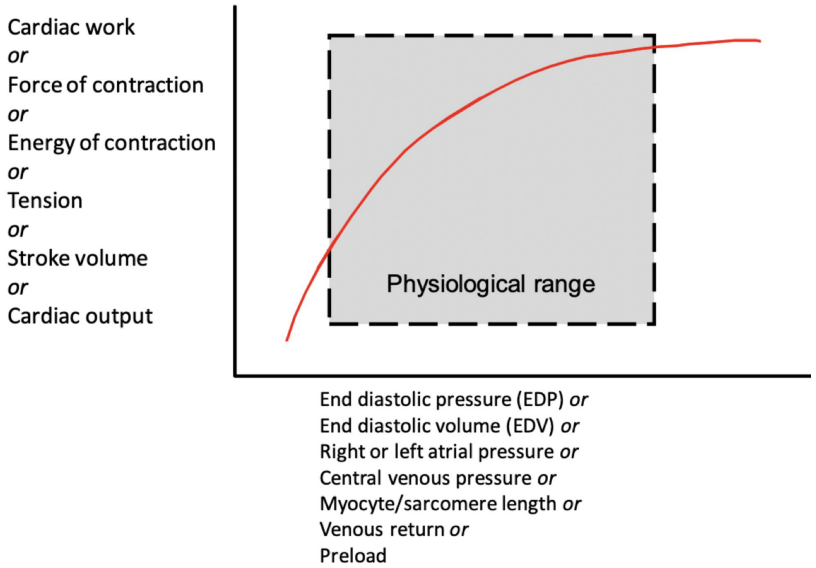
Control of Cardiac Output

Preload and Afterload

- CO must be able to be adjusted to different activities
  - Controlled by preload, afterload, contractility and heart rate
- Preload is the filling pressure of the heart determined by CVP
  - Function of EDV - degree of stretch of a ventricle before it contracts
- Afterload is the pressure the ventricle must overcome to pump blood into arteries determined by TPR
  - Mainly due to MABP

Frank Starling Mechanism

- Filling of the heart with more volume increases stretch which increases CO
- Cardiac Output/Stroke Volume is determined by EDV/EDP
- Amount of blood ventricle is pumping determines on amount of blood it is filled with
- This occurs due to increased actin-myosin overlap and increased cardiac myocyte calcium sensitivity
    - Calcium binds to troponin C → Tropnonin I moves away from actin and tropomyosin → Troponin T moves tropomyosin from actin
- Titin is a large protein which acts as a spring between myosin and actin, draws myosin inwards if sarcomeric length increases
    - Pulls on myosin binding protein C to increase crossbridges

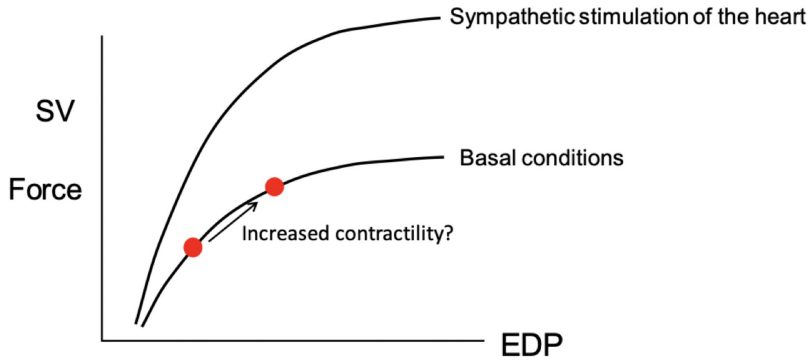


Consequences of Starling's Law

- 3 consequences
  - Stroke volumes of left and right ventricles are same
  - CVP will determine CO via preload
  - Maintains CO even if afterload increases or contractility changes
- Increase in CVP ⟶ Increase in right ventricular output ⟶ Increased blood in pulmonary veins ⟶ Increased filling of LA ⟶ Increased filling of LV and LVEDP ⟶ Increased SV ⟶ LV output matches RV output
- Right ventricle has a higher compliance - same degree of filling over lower range of pressures (low CVP required to fill RV)

Contractility

- Inotropy - force with which heart contracts due to calcium in myocytes
- Ability of heart to eject a SV at a given preload and afterload
- If contractility increases, new higher starling curve is produced where at any given preload there is more SV and force
- If contractility decreases, curve is lower (negative inotropy)
    - e.g. Heart Failure - decrease in contractility
    - Cardiac output falls to a point where it is insufficient to provide enough blood for body's metabolic needs



Effects of Afterload vs Preload

- Increased afterload should reduce stroke volume as ejection cannot begin until VP>AP, this point is delayed by greater afterload so less time for ejection
- Immediately: By starling response, if less time to eject blood → More blood stays in ventricle → LVEDP raised → Stroke volume increased by Frank-Starling mechanism
- Anrep response: Stretch due to increased LVEDV → Angiotensin II and endothelin released → Increase calcium transient over 10-15 minutes → Increased contractility so LVEDP moves back to initial level
- Long term: Heart becomes thicker by hypertrophy to pump more blood
- In normal range, afterload doesn't affect CO, but in aortic valve stenosis the pressure is so great that cardiac output falls

- Veins bring back to heart with low resistance facilitated by skeletal muscle pump and respiratory pump
- Preload = CVP which is determined by amount of blood in veins and capacitance
    - Venoconstriction increases CVP via SNS to pump more blood to tissues
        - e.g. in exercise
    - In haemorrhage, CVP decreases due to blood loss so venoconstriction, renal fluid retention and interstitial → plasma shift restore CO
- 20% of blood flows through through splanchnic veins which flow very slow so act as a reservoir of blood
    - In haemorrhage for example, venoconstriction causes mobilisation of blood from these reservoirs

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Control of Blood Pressure

Basics

- Blood pressure refers to pressure in the large arteries
  - Oscillates with cardiac cycle so can obtain systolic and diastolic values
- Blood pressure higher in arteries below heart compared to above heart
- Pressure waves increase in magnitude down arterial tree
- Flow wave pulsatile in aorta and smooths into microcirculation
  - Microcirculation should not be pulsatile as it would damage capillary beds
- Large arteries use 75% of blood flow to expand elastic fibres in walls and 25% is transported to tissues
  - During diastole, elastic recoil pushes blood flow through systemic circulation
- Difference in pressure between ABP and CVP drives circulation
  - Pressure decreases in resistance arteries
- Blood pressure is affected by many factors and depends on where it is measured

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Baroreceptor Reflex

- Baroreceptor reflex is mediated in cerebral cortex (Nucleus Tractus Solitarius) and is an ANS reflex involving both limbs of ANS
    - Reflex is located in upper part of body to protect brain circulation
    - Flow is determined by pressure, so pressure is regulated by this reflex
- Baroreceptors located in aortic arch (vagus) and carotid sinus (glossopharyngeal)
- Baroreceptor reflex can be moderated by altering BP set point, e.g. during exercise where higher BP is needed
    - Low BP detected and SNS stimulate
        - Arterial tone constricted → TPR increases → Afterload Increases → Increased SV
        - Venous tone constricted → Venous Capacitance increases → Preload increases → Cardiac Output Increases (Starling)
        - Heart rate and cardiac contractility increase → CO increases
    - BP = TPR x CO
        - Both TPR and CO increased so BP rises back to set point
- Adapts to new set point within few hours
- Primarily thought to be involved in short term regulation of BP but evidence to suggest some role in long term

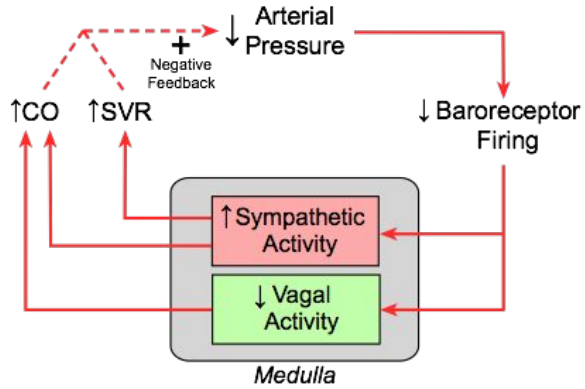

Figure 3. A sudden decrease in arterial pressure decreases baroreceptor firing, which activates sympathetic neurons and inactivates vagal neurons in the medulla. The resulting increases in CO and SVR act as a negative feedback mechanism to attenuate the fall in arterial pressure.

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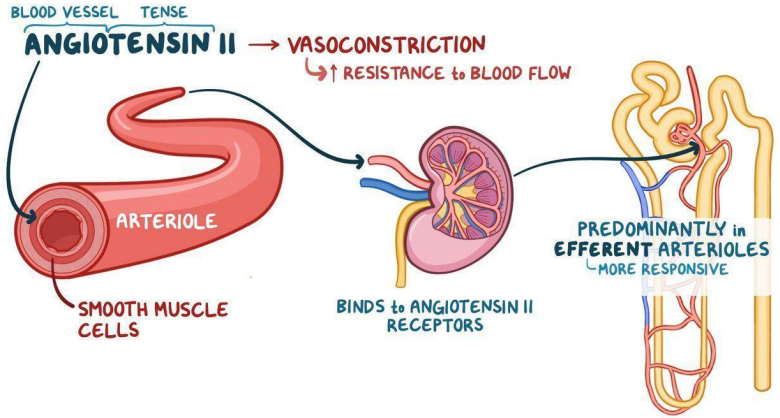
Renin-Angiotensin Aldosterone System

- Renin is a protein released by the kidney glomerulus when plasma volume is low
    1. Renin diffuses into plasma
    2. Activates angiotensinogen
    3. Angiotensin I cleaved
    4. ACE converts to angiotensin II
    5. Angiotensin II is a vasoconstricting factor
    6. Stimulates aldosterone release and ADH release
    7. Less Na+ excreted and water retained
    8. Blood volume and pressure increases
- Involved in long-term blood pressure control



Pressure Natriuresis

- Pressure Natriuresis is a response to high BP
- Increases blood flow through renal artery → More water and sodium excreted → Volume of ECS decreases → Decreased blood volume means decreased blood pressure

Control of Blood Flow

Basics

- Vascular tone is a result of balance between constricting and dilating influences
- Radius has the greatest influence on flow
- Endothelium cells are the lumen which line all blood vessels and are next to smooth muscle cells with gap junctions to them
- Resistance arteries have a 200um diameter and regulate resistance in vascular beds
- MABP drives flow through all organs and is regulated by baroreceptor reflex
- Autonomic nervous system limbs affects flow in most vascular beds by acting on receptors
    - Sympathetic nerve stimulation redistributes blood flow and increases TPR
    - Parasympathetic nerve stimulation only causes vasodilation in some arteries so no effect on TPR
- Chemicals such as adrenaline, angiotensin II and vasopressin also affect blood flow

Endothelin

1. Endothelin release stimulated by Angiotensin or Thrombin in pathological conditions
2. Binds to ETA receptor on smooth muscle
3. Causes contraction of smooth muscle

Nitric Oxide

1. Bradykinin, histamine or ATP binds to receptor
2. Calcium concentration increases
3. eNOS converts L-arginine to NO
4. Nitric Oxide can diffuse directly into SM cells
5. Activates Guanylate Cyclase: GTP becomes cGMP
6. cGMP causes hyperpolarisation of membrane via potassium channels and restoration of calcium

Endothelium Derived Hyperpolarisation

1. Sheer forces/Vasodilators such as bradykinin bind to receptor
2. Increase [Ca^{2+}]
3. Ca^{2+} activated K+ channel opens
4. K+ flood into cell and hyperpolarises membrane
5. Conducted through gap junctions into SM cell
6. EETs and Hydrogen Peroxide also released from endothelium which opens K+ channels on SM cell

Autoregulation

- Myogenic response due to stretch activated ion channels in SM membrane
  - Any stretch in arteries due to increased pressure causes constriction to maintain flow and vice versa
  - Stretch causes opening of sodium channels to depolarise and open VGCCs
  - Particularly important in heart, brain and kidneys
- Metabolism produces vasodilating factors which cause local dilation
  - Vasodilatation only occurs in contracting muscle, as in all other vessels, metabolites are washed away by blood flow
  - During exercise, vasodilating metabolites accumulate in muscle and heart causing vasodilation to increase blood flow
  - Metabolic hyperaemia allows tissues to control their own blood flow
- Reactive hyperaemia occurs after static exercise - Vasodilating metabolites accumulate when blood flow to muscle occluded during maintained contraction and when released, metabolites washed away and vascular tone re-established

Fluid Balance

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Fluid Balance in the Microcirculation

Types of capillary:

- Continuous - endothelium covers entire surface with tight junctions between cells
- Fenestrated - endothelial cells contain pores
- Sinusoidal - spaces exist between endothelial cells

Starling principle: $J_v = (P_{cap} - P_{int}) - \sigma(\pi_{cap} - \pi_{int})$

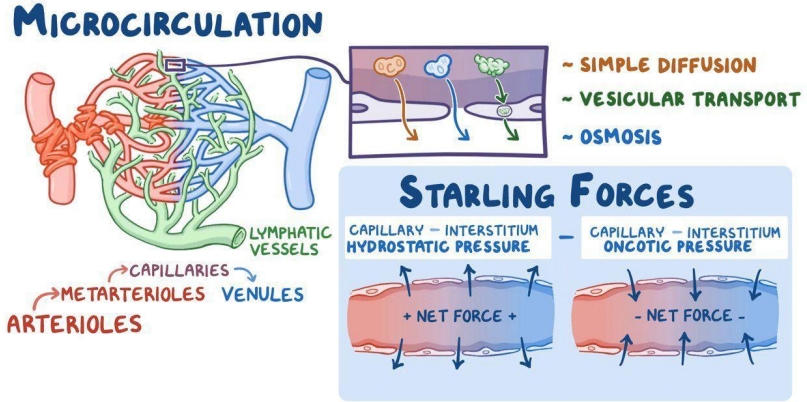
- Overall it favours filtration but is dynamic and locally variable

Oedema can occur due to 4 main factors

- Increased P_{cap} - e.g. in HF, venous pressure increases and backs up into capillaries
- Increased capillary or venular permeability - e.g. in inflammation so proteins can leak into interstitial space reducing absorption
- Decreased π_{cap}
- Lymphatic obstruction

There is a net filtration of 2-4 litres a day by entire microcirculation

- Excess is returned to blood stream via lymphatic system
- If net filtration increases and fluid accumulates then causes oedema



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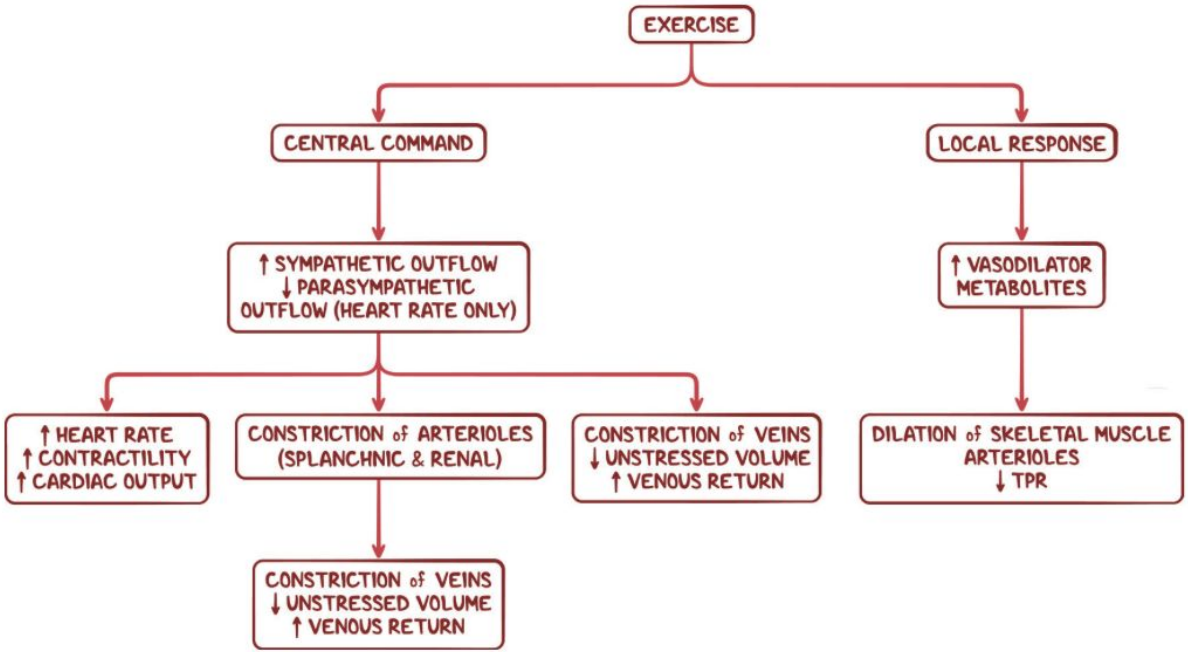
Orthostasis and Exercise

Orthostasis

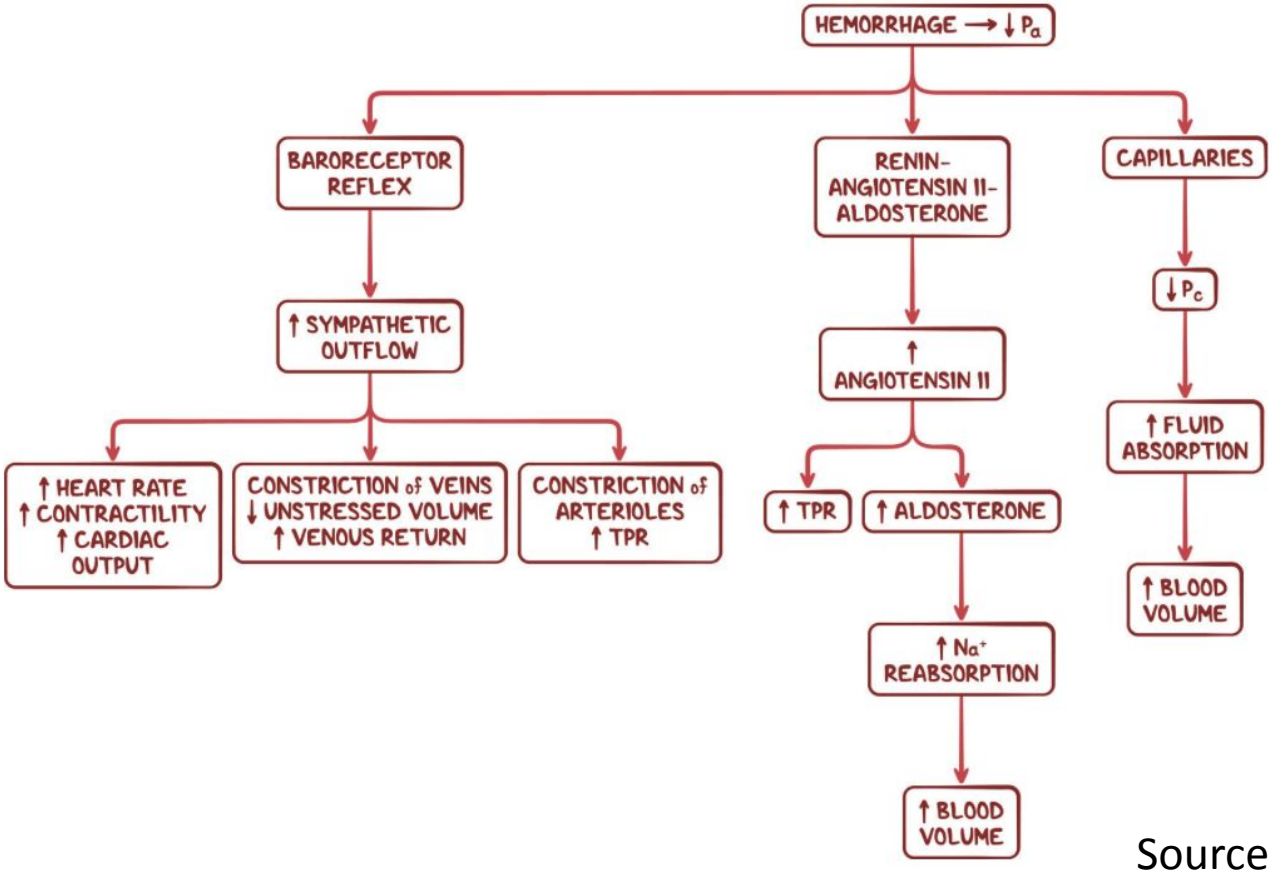
- Standing up causes a redistribution of blood volume towards the lower extremities, most of which occurs in the veins. Arterial and venous blood pressures increase and decrease, respectively, in the lower and upper parts of the body.
- The redistribution of blood causes an immediate fall in central venous pressure which reduces cardiac output and leads to an increase in filtration in the lower extremities which further diminishes CVP by decreasing blood volume.
- Compensatory mechanisms which limit the fall in cardiac output and a consequent decrease in cerebral blood flow include the baroreceptor reflex, a veno-arteriolar axon reflex, and the skeletal muscle pump.
- Standing, especially if prolonged and in a hot environment, can cause a vasovagal faint due to a sudden bradycardia and vasodilatation thought to be induced by the Bezold-Jarisch reflex.

Exercise



Source: Osmosis

Haemorrhage



Source: Osmosis

Questions?

SBAs

The fun bit!

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Question 1

What does the second heart sound (S2) correlate to?

a. Opening of the AV valves
b. Closure of the AV valves
c. Opening of the semilunar valves
d. Closure of the semilunar valves

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c. Opening of the semilunar valves
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Question 2

A 69 year-old gentleman presents with a range of symptoms indicative of heart failure, including dyspnoea (shortness of breath) and peripheral oedema. Which of the following constitutes a reason for oedema in heart failure?

a) Increased secretion of anti-natriuretic peptide (ANP)
b) Reduced aortic pressure
c) Increased glomerular filtration rate
d) Reduced activation of the renin-angiotensin-aldosterone system (RAAS)
e) Increased secretion of anti-diuretic hormone (ADH)

Question 2

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c) Increased glomerular filtration rate
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e) Increased secretion of anti-diuretic hormone (ADH)

Question 4

A 40 year old lady was running for the bus. As a result of the additional sympathetic output to her heart, positive inotropy and chronotropy would be observed in her left ventricle. What changes would you expect to occur with respect to her left ventricle?

a) Only the systolic pressure, stroke volume and stroke work increase
b) The systolic pressure, stroke volume, stroke work and heart rate decrease
c) The systolic pressure, stroke volume, stroke work and heart rate increase, while the end-systolic and diastolic volume decrease
d) The systolic pressure increases only
e) Only the systolic pressure and stroke volume increase

Question 4

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e) Only the systolic pressure and stroke volume increase

Question 5

Cardiac catheterisation was carried out on a 60-year-old patient to determine his ventricular function, as he was experiencing shortness of breath on exertion whilst climbing a flight of stairs. What parameter is the best representation of preload?

a. Mean Arterial Pressure
b. End-Diastolic Volume
c. End-Systolic Volume
d. Central Venous Pressure
e. Arterial Elastance

Question 5

Cardiac catheterisation was carried out on a 60-year-old patient to determine his ventricular function, as he was experiencing shortness of breath on exertion whilst climbing a flight of stairs. What parameter is the best representation of preload?

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c. End-Systolic Volume
d. Central Venous Pressure
e. Arterial Elastance

Question 6

Which of the following options correctly identifies the changes which occur during a sudden decrease in blood pressure?

a) Increased vasoconstriction, increased heart rate, decreased force of myocardial contraction
b) Increased vasodilation, increased heart rate, increased force of myocardial contraction
c) Increased vasoconstriction, decreased heart rate, increased force of myocardial contraction
d) Increased vasodilation, decreased heart rate, decreased force of myocardial contraction
e) Increased vasoconstriction, increased heart rate, increased force of myocardial contraction

Question 6

Which of the following options correctly identifies the changes which occur during a sudden decrease in blood pressure?

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b) Increased vasodilation, increased heart rate, increased force of myocardial contraction

c) Increased vasoconstriction, decreased heart rate, increased force of myocardial contraction

d) Increased vasodilation, decreased heart rate, decreased force of myocardial contraction

e) Increased vasoconstriction, increased heart rate, increased force of myocardial contraction

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Questions?

Sources:

- Lectures
- Osmosis
- Zero To Finals
- TeachMePhysiology

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Thank you for attending the session -

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