YO! Physiologer dudes

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Many of my friends have found these notes useful in their study for Physiology 1A.

But before you take a look at them and start cramming as if your life depends on it, take a moment to meet the God that created a universe that is so complex and worthy of study, yet knows you and I personally:

Psalm 139:13-14 - "For you created my inmost being; you knit me together in my mother's womb. I praise you because I am fearfully and wonderfully made; your works are wonderful, I know that full well."

Check it out sonnnnnn!: http://www.matthiasmedia.com.au/2wtl/

1 Lecture 1

1.1 Understand the functions of the CVS

1. **Main function** is to **supply** O_2**/nutrients** and **remove** CO_2**/waste products** (occurs at level of capillaries).
2. **Heart** performs **sensory** and **endocrine function**s that **regulate blood pressure/volume**.
3. **Blood vessels regulate blood pressure** and **distribution** to various body parts.
4. **Blood** carries **hormones/other substances** to tissues.

1.2 Describe the path of blood flow through the heart and vasculature

The cardiovascular system consists of **two circuits**:

1. Pulmonary circulation

1. **Deoxygenated blood** from the upper/lower body enter the **right atrium** via the **superior** and **inferior vena cava** respectively.
2. The right atrium then pumps the blood past the **tricuspid valve** into the **right ventricle**.
3. The right ventricle contracts, pumping blood through the **pulmonary (semi-lunar) valve** to the **lungs** via the **pulmonary artery**.
4. **Oxygenated blood** returns from the lungs and flows through the **pulmonary vein** into the **left atrium**.

2. Systemic circulation

1. The **left atrium** pumps blood past the **mitral (bicuspid) valve** into the **left ventricle**.
2. The **left ventricle** contracts, pumping blood past the **aortic (semi-lunar valve)** into the **aortic trunk** from which the **systemic arteries** extend.
3. These arteries further branch off into **small arteries**, then **arterioles** and then **capillaries**.
4. The capillaries then unite to form larger **venules** which unite to form the **small** and then the **large veins**.

1.2.1 Important notes

- There is **no direct communication** between the atria or ventricles because they are separated by the **interatrial** and **interventricular septa** respectively. Blood can only enter the ventricles via their respective atria.
- The level of circulation at which arterioles, capillaries and venules exist, is called the **microcirculation** or small vessels.
- The passage, circuits and microcirculation are pictured in Figure 1 on the next page.
- The aortic pressure varies between a high point during **ventricular systole** ($\approx 120\,\text{mmHg}$), and a low point during **ventricular diastole** ($\approx 80\,\text{mmHg}$), written 120/80. This yields a **mean aortic pressure** of $\approx 90\,\text{mmHg}$.
- **Arteries** carry blood **away** from the heart.
- **Veins** carry blood **toward** the heart.
- All arteries and veins carry oxygenated and deoxygenated blood respectively **except the pulmonary vessels where the opposite occurs** explaining why the **pulmonary arterial pressure** is only $\sim 15\,\text{mmHg}$.

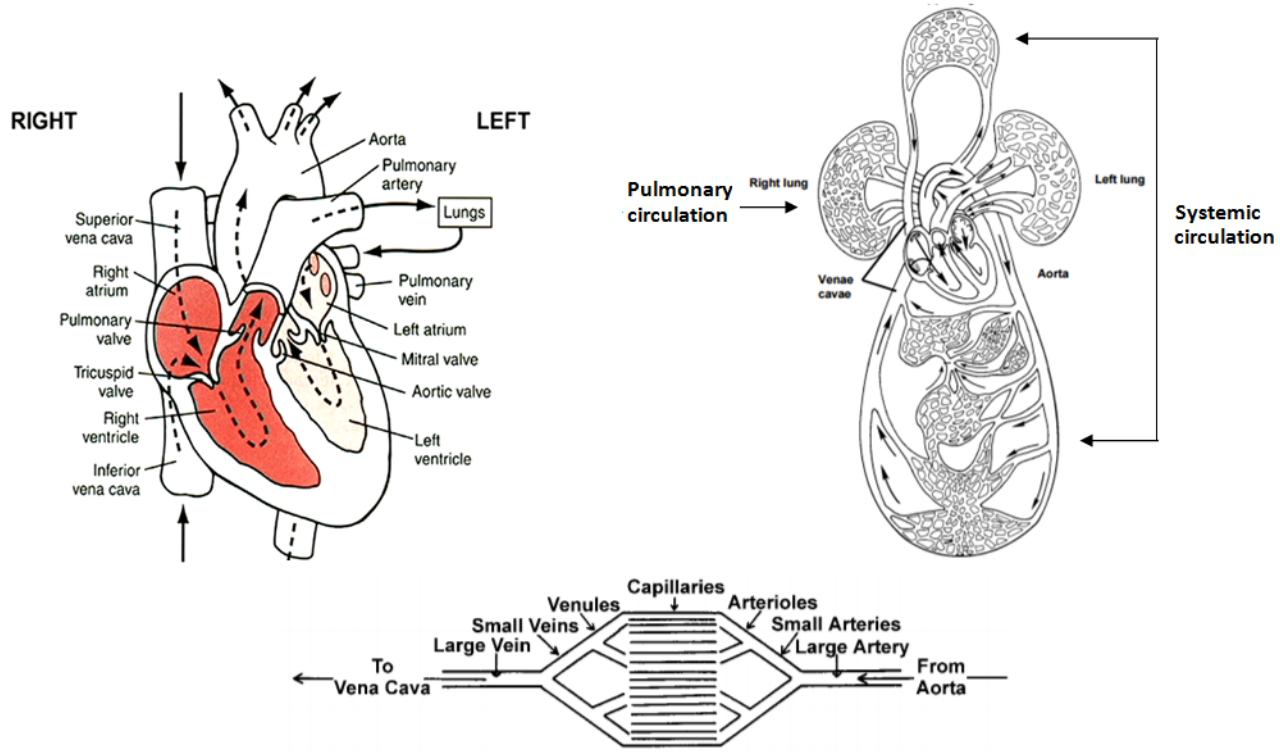


Figure 1: Path of blood (left), two different circuits (right), microcirculation (middle)

1.3 Name the different valves in the heart and understand how they operate

The heart contains flaps of endocardium with an inner framework of fibrous connective tissue called **valves** that only permit **unidirectional flow**. There are two main types:

1. Atrioventricular (AV) valves

- To prevent backflow of blood from the ventricles into the atria, the **AV valves** guard the opening between the atria and the ventricles.
- These valves are connected to the **papillary muscles** via the **chordae tendineae** which prevent them from being sucked into the atria.
- **Biscuspid** bicycles ride their bicycles on the **left** side of the road. The **third** exit (**tricuspid valves**) at a roundabout is always the **right**.

2. Semilunar valves

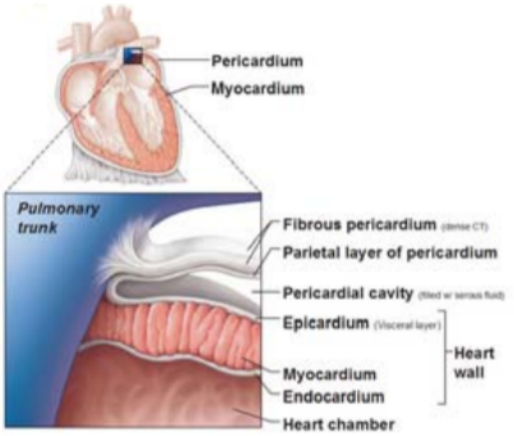
- To prevent ventricular backflow, the **semi-lunar** valves guard the ventricular openings to the large vessels.
- The **pulmonary valve** guards the opening between the **right ventricle** and the **pulmonary artery**.
- The **aortic valve** guards the opening between the **left ventricle** and the **aorta**.
- Both of these valves are **tricuspid**.

The **passive** opening and closing of these valves is a consequence of **pressure gradients**.

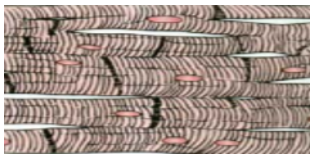
- When the blood is **behind** the valve, a **forward pressure gradient** is generated, **opening** the valve.
- When the blood is **ahead of** the valve, a **backward pressure gradient** is generated, **closing** the valve.

1.4 Understand the physiology of the cardiac muscle

- The heart consists of **3 layers**: **outer**, **middle** and **inner endocardium**.
- The **myocardium** contains **atrial**, **ventricular** and specialised excitatory/conductive fibres.
- The ventricular muscle is much thicker than the atrial muscle.
- The left ventricular muscle is much thicker than the right because it needs to pump to all the organs (**systemic circulation**) whilst the right only needs to pump to the lungs (**pulmonary circulation**).
- The specialised fibres don't have many contractile fibres and their **contraction is feeble** in comparison with the atrial/ventricular muscle, but exhibit **rhythmicity** and varying **conduction rates**.



- **Striated** cardiac muscle fibres are arranged in a **latticework**.
- **Intercalated discs** are formed when the membranes of cardiac myocytes meet end to end, serving as **permeable communicating gap junctions** that are **low resistance bridges** that allow for the **rapid spread of excitation**.
- Hence, they act as a **syncytium** (single unit).
- The heart has an **atrial** and a **ventricular** syncytium. This is to ensure that the atria contract a short time before the ventricles so that the ventricles have enough time to fill before pumping.



1.5 Describe the nervous supply (ANS) to the heart

- The **sympathetic nerves increase** the volume of pumped blood $\sim 100\%$ by:
  1. **Increasing heart rate** from 70 up to 200 bpm.
  2. **Increasing contractile force**
- The **parasympathetic nerves (vagus) decrease** the volume of pumped blood $\sim 50\%$ by:
  1. **Decreasing heart rate** $\sim 60\%$.
  2. **Decreasing contractile force** $\sim 25\%$.

1.6 Define cardiac output

- **Cardiac output** (CO) is the product of **heart rate** (on average, 70 beats/min) and **stroke volume** (volume of blood ejected by left ventricle per beat) [on average 70 mL/beat].

$$CO = HR \times SV$$
$$\overline{CO} = 70\,\text{beats/min} \times 70\,\text{ml/beat} \approx 5\,\text{L/min}$$

1.7 Describe the distribution of systemic blood flow at rest and during exercise

- During exercise, the **brain**, **liver/GIT**, **kidneys** receive the same amount of blood as at rest (you don't want to be pooing/peeing everywhere).
- The **skeletal muscle**, **skin** and **heart** receive more blood during exercise because the muscles and heart need more O_2 and you need to lose generated heat via convection.
- The **skeleton, marrow** and **fat** receive a **reduced blood supply**.

Organ	At Rest (5l/min)	Exercise (25l/min)
Brain	13-15% (750ml)	3-4% (750ml)
Heart	4-5% (250ml)	4-5% (1250ml)
Liver & GIT	20-25% (1250ml)	3-5% (1250ml)
Kidneys	20% (1000ml)	2-4% (1000ml)
Muscle	15-20% (1000ml)	70-80% (18,000ml)
Skin	3-6% (300ml)	13-15% (3,500ml)
Skeleton, marrow & fat	10-15% (750ml)	1-2% (500ml)

2 Lecture 2

2.1 Describe the various components of the vasculature

2.2 Describe the unique characteristics of the different types of vessels in terms of both structure and function

- Blood travels in a **circular pattern** through the **vasculature**.
- The components of the vasculature are described below and their structure and function related.
- Note that **compliance** C is the change in **volume** due to a given change in **pressure**, $C = \frac{\Delta V}{\Delta P}$

2.2.1 Arteries

- Arteries **conduct** blood **away** from the **heart** to tissues.
- Because of their relatively **thick**, **elastic** walls, arteries have **low compliances** because **small increases** in **blood volume** result in **large increases** in **blood pressure**.
- Hence, they function as **pressure reservoirs** which **stretch** during **systole** and **withstand high pressures** and then **recoil** during **diastole**.
- Significant pressure is released resulting in **high pressure blood transport**.

2.2.2 Arterioles

- Arterioles are the finest division of the arterial tree, **containing more smooth muscle** and **smaller diameters**.
- Thus, they represent a **major resistance** and act as **control conduits** through which blood is **released into the capillaries** depending on the **contractile state** of the **smooth muscle** as dictated by the **ANS**.

2.2.3 Capillaries

- Capillaries only consist of a **single layer** of **endothelial cells** permeable to **small molecular substances** facilitating **substance exchange** via **simple diffusion** and a **basement membrane** imparting **rigidity**.
- Represent a **major resistance** as the internal diameter is only $\sim$ that of an erythrocyte slowing bloodflow to ~ 0.1 mm/s, have **no smooth muscle** or **elastic tissue**.
- Are the **most numerous** and are found in **larger quantities** in **metabolically active** tissues.

2.2.4 Venules/Veins

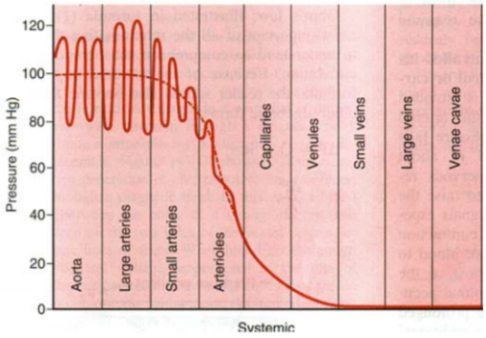
- Venules collect blood from capillaries and converge to form **veins**.
- Venules contain **negligible smooth muscle**, but **veins** contain some, albeit much **less** than arteries, resulting in **thinner walls** and thus **larger internal diameters**.
- These means **veins** have **high compliance** and act as a **low resistance** return vessel and a **blood reservoir**.

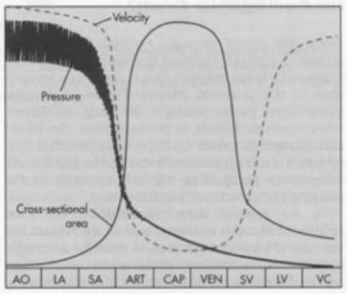
2.2.5 Lymphatic Vessels

- The **lymphatic system** is a network of vessels that allows fluid leaking from the capillaries to ultimately drain back into the venous system.

2.3 Describe changes in pressure, velocity of flow and cross-sectional area that are seen across the vasculature

- The **aortic pressure** is the highest and oscillates between the **systolic** and **diastolic** pressure. The pressure slowly dips as the blood passes through the **large arteries** and then plummets as it enters the **small arteries/arterioles**.
- The pressure in the **capillaries** is highly variable; 35 mmHg on the arteriolar side and $\sim$ 10 mmHg on the venous end.
- The blood pressure becomes **negligible** as it reaches the **veins**.
- The blood flow **velocity** is **inversely proportional** to the **total cross sectional area** of a component of vasculature.
- Hence, the velocity is the slowest in capillaries because it has the highest total cross sectional area of any other vessel type in the body.





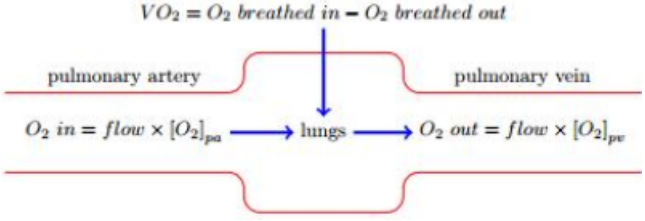
2.4 Understand the use of the Fick principle and the indicator dilution technique in measuring cardiac output

2.4.1 Fick Principle

- The **Fick principle** measures cardiac output based on the,
  1. Volume of O_2 absorbed from the lungs into the pulmonary blood per minute or VO_2.
  2. The concentration of O_2 in the blood leaving the right heart via the pulmonary artery $[O_2]_{pa}$.
  3. The concentration of O_2 in the blood entering the left heart via the pulmonary vein $[O_2]_{pv}$.

$$VO_2 = CO[O_2]_{pv} - CO[O_2]_{pa}$$
$$CO = \frac{VO_2}{[O_2]_{pv} - [O_2]_{pa}}$$

- On average, $[O_2]_{pa}$ = 160 mL/L, $[O_2]_{pv}$ = 200 mL/L and VO_2 = 200 mL resulting in an average cardiac output of $\sim$ 5 L/min.



2.4.2 Indicator Dilution Technique

- Concentration c is given by,

$$c = \frac{m}{V} = \frac{\frac{dm}{dt}}{\frac{dV}{dt}} \qquad \Rightarrow \qquad dm = \frac{dV}{dt} c\,dt \qquad m = CO \int_0^T c\,dt$$

$$\therefore \boxed{CO = \frac{m}{\int_0^T c\,dt}}$$

- A known mass of dye m is injected into a large vein/right atrium. From there, it passes through the right side of the heart, lungs and left side of the heart into the arterial system.
- The dye concentration c in a peripheral artery is then plotted over a time period $[0, T]$.
- The cardiac output CO is then determined by integrating this curve and evaluating the above expression. In this course c is taken as a constant or **average concentration of dye** where $[0, T]$ is the interval over which this average c occurs.

2.5 Understand how different indicators can be used to measure different volumes

- Unlike in the previous dotpoint in which dilution was used to measure cardiac output, bodily compartments are virtually closed systems.
- Hence, the volume V of any compartment can be determined by injecting a known mass m of indicator that is not metabolised or excreted, into the compartment, allowing it to disperse evenly in the compartment and only that compartment.
- The concentration c of the indicator is then measured and the volume calculated using,

$$\boxed{V = \frac{m}{c}}$$

Specific indicators are used to measure the volumes of specific compartments:

- **Plasma volume**: ^{131}I labelled albumin or Evans Blue dye.
- **Extracellular volume**: Inulin
- **Interstitial fluid volume** = extracellular volume - blood volume
- **Total body water**: Radioactive water (tritium ^3H_2O) or heavy water (deuterium ^2H_2O).
- **Red cells**: Radioactive chromium (^{51}Cr)

3 Lecture 3

3.1 Describe the path of action potentials through the conduction system of the heart

Pre-knowledge

- For the heart to pump blood effectively, the cardiac muscle must contract in a highly synchronised manner; the atria together, then a short time after, the ventricles together. Cardiac muscle requires no CNS input because the heart is **autorhythmic**, i.e. it contains a specialised system for generating impulses which triggers its own **rhythmical contractions**. Once generated, these impulses are rapidly conducted throughout the heart along a specific pathway.

Pathway

1. The **sinoatrial (SA) node** is a flattened strip of specialised cardiomyocytes in the lateral wall of the upper right atrium. It has the fastest inherent rate of spontaneous depolarisation ($\sim$ 70 times/min) and hence functions as the pacemaker; the origin electrical impulses.
2. The **atrioventricular (AV) node** is a small bundle of specialised cardiomyocytes at the base of the right atrium. Impulses generated by the SA node spread to the **atria** via **interatrial pathways** and then to the **AV node** through **internodal pathways** $\pm$30 ms following its generation in the **SA node**.
3. $\pm$100 ms following its arrival at the AV node **(AV nodal delay)**, the impulse arrives at the interventricular septum via the **atrioventricular bundle** or **bundle of His**.
4. $\pm$40 ms following its arrival at the bundle of His, the impulse divides into the **right** and **left bundle branches** which travel down the septum, curve around the tips of the ventricles and travel back towards the atria.
5. These bundle fibres end in the **purkinje fibres**. **large elongated cylindrical cells** with **numerous mitochondria** and **few myofibrils** specialised for **fast conduction**. Here the impulse is transmitted through the entire ventricular muscle mass via gap junctions between individual ventricular fibres.

Things to note:

- The **rate of conduction increases** with each successive location in the conducting pathway.
- The **rate of discharge decreases** with each successive location in the conducting pathway. If the SA node is damaged, autorhythmic cells in the other nodes or bundles can take over albeit none discharge as quickly as the SA node.

3.2 Understand the ionic basis of the different phases of the pacemaker potential

Table 1: Intracellular and extracellular concentrations of ions involved in cardiac potentials

Ion	ICC (mM)	ECC (mM)
Na^+	15	150
K^+	150	15
Ca^{++}	low	high

From Table 1,

- Na^+ wants to **influx** to **depolarise** the cell.
- K^+ wants to **efflux** to hyperpolarise the cell.
- Ca^{++} wants to **influx** to **depolarise** the cell.

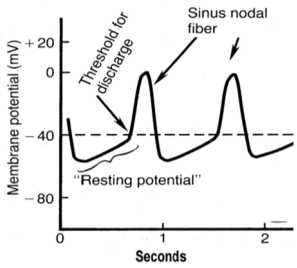


Figure 2: Action potential recorded from a sinus nodal fibre

The pacemaker potential consists of **three main phases**,

1. **Slow depolarisation (-60 to -40 mV)**
   - K^+ channels slowly close (permeability decrease) $\Rightarrow$ K^+ efflux halts.
   - Constant Na^+ influx
   - T Ca^{++} channels slowly open (permeability increase) $\Rightarrow$ Ca^{++} influx.
2. **Depolarisation/upstroke (-40 to 0 mV)**
   - At -40 mV, threshold is reached.
   - L (long lasting) Ca^{++} channels open (huge permeability increase) $\Rightarrow$ huge Ca^{++} influx
3. **Repolarisation (0 to -60 mV)**
   - Both Ca^{++} channel types close (permeability decrease), Ca^{++} influx halts.
   - K^+ channels open (permeability increase) $\Rightarrow$ K^+ efflux.

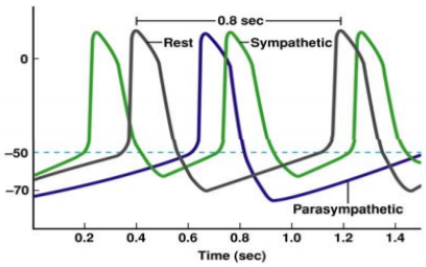
3.3 Describe the effects of the ANS on pacemaker potentials

The **SA node** receives direct input from the **ANS**.

- **Sympathetic nervous activity** increases the frequency of generated action potentials and hence the heart rate by,
  1. **increasing slope** of spontaneous depolarisation.
  2. **decreasing level of repolarisation**

  so that threshold is reached more easily.
- **Parasympathetic nervous activity** decreases the frequency of generated action potentials and hence heart rate by,
  1. **decreasing slope** of spontaneous depolarisation.
  2. **hyperpolarising membrane potential**

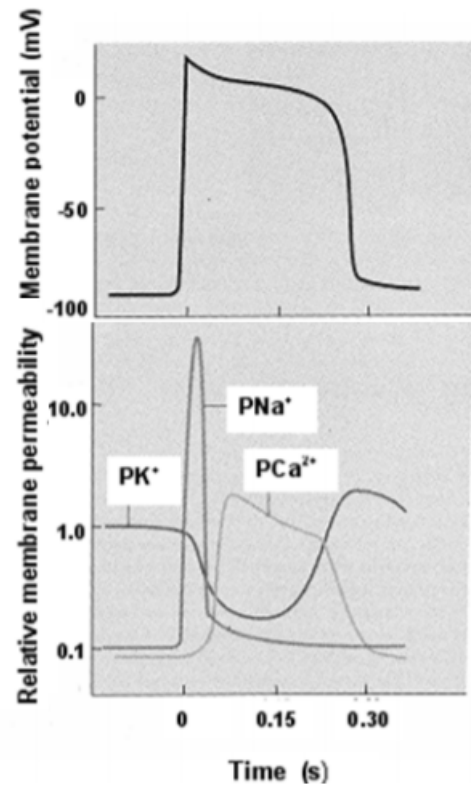
  so that threshold is reached less easily.



3.4 Understand the ionic basis of the different phases of the ventricular action potential

Note: Permeability of an ion Z will be referred to as P_Z from now on.
The **ventricular action potential** consists of **four main phases**,

1. **Resting state (~ -90 mV)**
   - $P_{K^+} > P_{Na^+} \Rightarrow K^+$ efflux $\Rightarrow$ RMP $\sim$ -90 mV.
2. **Depolarisation/Fast upstroke ($\sim +30$ mV)**
   - Na^+ channels open (huge permeability increase) $\Rightarrow$ Huge Na^+ influx.
   - K^+ channels close $\Rightarrow K^+$ efflux halts.
3. **Plateau phase (Refractory period)**
   - Na^+ close quickly (permeability increase is very transient).
   - K^+ channels open (high permeability) $\Rightarrow K^+$ efflux.
   - Both of these cause the membrane potential to fall slightly but the membrane remains depolarised at a plateau of ~ 0 mV for up to 300 ms because,
     - Slow Ca^{++} channels open $\Rightarrow$ slow Ca^{++} influx,
     - and K^+ channels close $\Rightarrow$ reduced K^+ efflux.
4. **Repolarisation**
   - Ca^{++} channels close $\Rightarrow$ reduced Ca^{++} influx.
   - K^+ channels open $\Rightarrow$ huge K^+ influx.

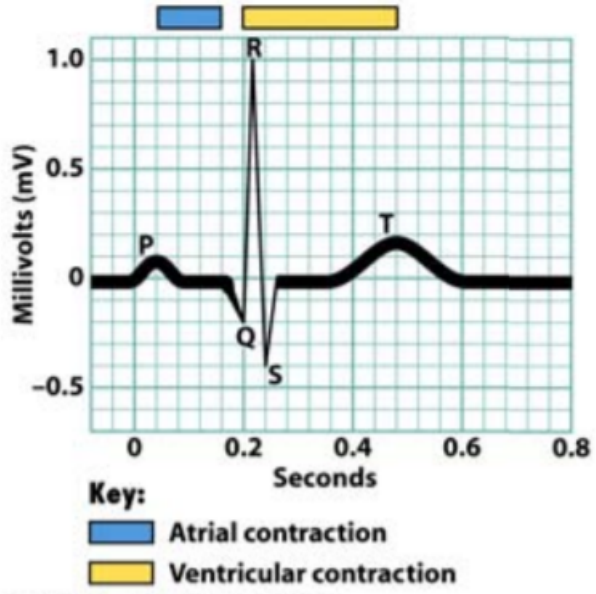


3.5 Describe the different waves of the electrocardiogram and how they relate to the events of the cardiac cycle

- **P wave**: atrial depolarisation
- **QRS complex**: ventricular depolarisation
- **T wave**: ventricular repolarisation

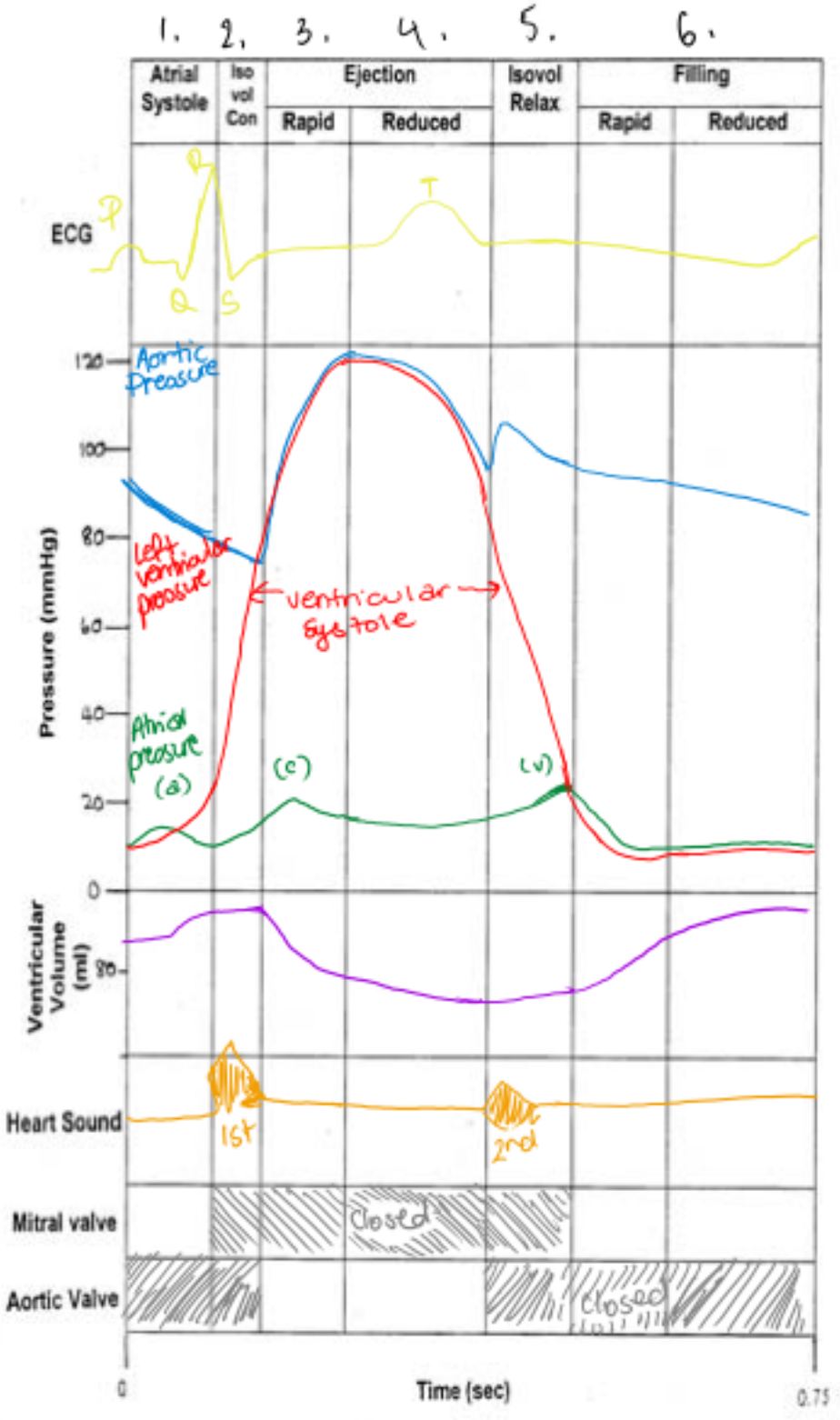
Note:

- Atrial repolarisation is not evident on the ECG because it occurs at the same time as ventricular depolarisation.
- Between waves is an **isoelectric line**



4 Lecture 4

4.0.1 Understand the different phases of the cardiac cycle and how the parameters vary in each of the phases

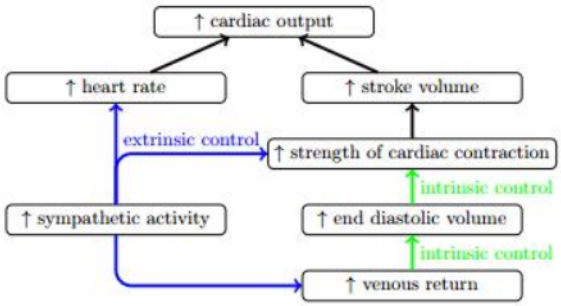


1. **Atrial systole**
    - **SA Node** initiates electrical activity which spreads through the **atria** (P wave in ECG).
    - **Atrial pressure** increases because of following atrial contraction.
    - $P_{atria} > P_{ventricle} \Rightarrow$ mitral valve opens. The **aortic valve** remains closed because ejection is not desired until the ventricular end-diastolic volume is reached.
    - Blood is pushed into the ventricle resulting in an increase in ventricular pressure and volume.
    - The **aortic pressure** continues to fall as the aortic valve is closed meaning no blood can enter the aorta and whatever blood is in the aorta is being drained to the other vessels.
2. **Ventricular excitation & isochoric ventricular contraction**
    - Electrical activity spreads through the ventricles (**QRS Complex**) causing contraction and abrupt increase **ventricular pressure**.
    - $P_{ventricle} > P_{atria} \Rightarrow$ mitral valve closes causing **first heart sound**.
    - The ventricle is now a closed chamber which is contracting further **increasing ventricular pressure** but is **isochoric** because all valves are closed.
    - Isochoric contraction causes bulging of AV valves into the atria resulting in a **small sharp increase** in **atrial pressure** (c wave).
    - **Aortic pressure** continues to fall.
3. **Rapid ejection phase**
    - $P_{ventricle}$ rises until $P_{ventricle} > P_{aorta}$ causing the **aortic valve to open** and **ventricular ejection** to begin.
    - **70% is emptied in the first third of the ejection phase**.
    - **Ventricular pressure** peaks, 120 mmHg in LV and 25 mmHg in RV.
    - **Aortic pressure** peaks as blood is ejected into the aorta.
    - **Atrial pressure** decreases as the AV valves no longer bulge into the atra.
4. **Reduced ejection phase (end of ventricular systole)**
    - **Remaining 30% emptied** decreasing **ventricular volume**.
    - **Contractile forces** decrease with the **intraventricular pressure**.
    - Blood flow decreases with **aortic pressure**.
    - **Repolarisation** of myocardium occurs (T wave in ECG).
    - Blood begins to flow back into the atria slightly **increasing atrial pressure**.
5. **Isochoric relaxation**
    - Ventricular relaxation begins decreasing **intraventricular pressure rapidly**.
    - The pressure in the large arteries push blood back towards the ventricles causing the **aortic** and **pulmonary valves** to close causing **second heart sound**.
    - A small oscillation is caused on the falling phase of the aortic pulse wave due to the closing of the aortic valve (**dicrotic notch**).
    - Both valves are closed and no blood leaves or enters. The **ventricular volume** is at its minimum (**end systolic volume**).
    - This causes the **ventricular pressure** to decrease but causes no change in volume because the system is isochoric.
    - Blood begins to flow into the atria increasing **atrial pressure** (v wave).
6. **Rapid & reduced filling phases**
    - $P_{atria} > P_{ventricle}$ causing the AV valves to open whilst the aortic and pulmonary valves remain closed.

- Blood fills ventricles from the atria, **decreasing atrial pressure** and **slightly increasing ventricular volume** but the **ventricular pressure** remains low because the filling is slow.
- **Aortic pressure** as blood in aorta is drained away.
- **Atrial depolarisation starts and the cycle repeats**.

5 Lecture 5

5.1 Know the factors altering cardiac output



5.2 Understand Starling's Law of the Heart and the effects of preload and afterload on cardiac output

Preload is the **end diastolic volume (EDV)**. A higher EDV causes higher ventricular pre-stretching, increasing the overlap potential of the thick and thin filaments. The EDV is determined primarily by the **venous return** which is determined by the following factors.

- **Right atrial pressure**: The peripheral venous pressure is very low after it exits the capillaries. The higher the right atrial pressure, the larger the pressure that the venous blood is opposing, significantly decreasing venous return.
- **Increasing blood volume** via increased fluid consumption can be enough to raise venous pressure, forcing more blood into the heart during diastole.
- **Venous tone**: Sympathetic input stimulates venous smooth muscle to contract, decreasing the capacity of the veins to store blood and increasing venous return.
- **Bodily pumps**: The **thoracic pump** increases venous return during inspiration because of the established negative thoracic pressure and thus increased pressure gradient for bloodflow towards the heart.The **abdominal pump** increases the pressure gradient towards the heart by increasing abdominal pressure, compressing veins in the region. The **skeletal muscle pump** clamps veins increasing the pressure gradient towards the heart.

Afterload is the pressure required to open the **aortic/pulmonary valves** also known as the **peripheral resistance**.

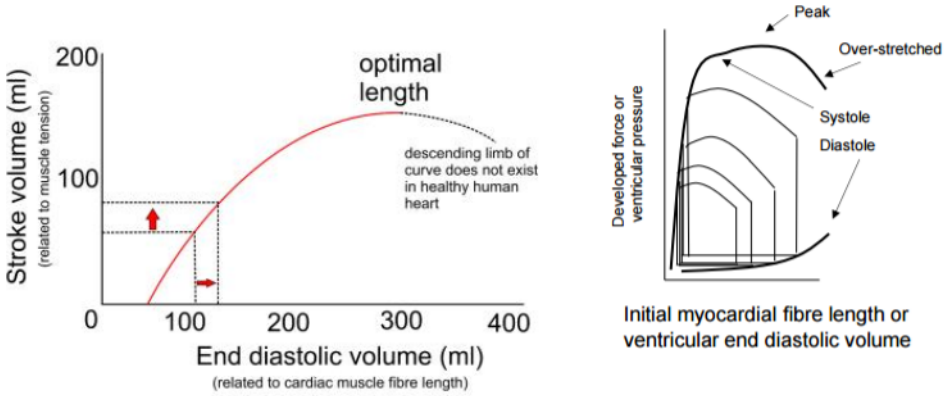
- The higher the afterload, the higher the pressure required to open the aortic valve. This means that more contractile energy is devoted to opening the aortic valve rather than ejecting the blood, decreasing the **end systolic volume (ESV)**. Because $SV = EDV - ESV$, the stroke volume is decreased.
- The **Ratio stroke volume** or **ejection fraction**

$$EF = \frac{SV}{EDV}$$

  quantifies the proportion of the heart's contents that is ejected with each cycle. A healthy $EF \sim 55\%$.

The Frank-Starling law of the heart states that: *energy of ventricular contraction is a function of the initial length of the ventricular fibres* or that the **ventricular automatically adjusts to an increased EDV by increasing the force of contraction**.

- This ensures that the EF is approximately constant over a wide range of EDV values (blood in = blood out).
- The stroke volume however only increases with EDV to a point, whereby any further stretching causes damage and a reduction in SV.



5.3 Understand that heart rate is controlled by the ANS and adrenaline

The **heart rate** is controlled via two main avenues:

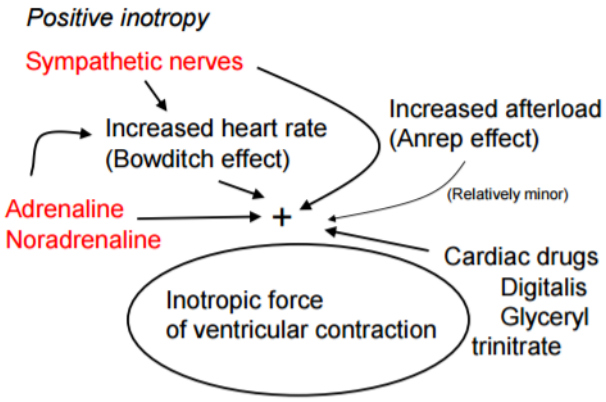
1. **Neural control**
    - Increased activity via the **sympathetic neurons** to the SA node increase the frequency of action potentials in the pacemaker cells by releasing **noradrenaline** that results in the opening of funny and T-type Ca^{++} channels resulting in a decrease in the slope of spontaneous depolarisation and decrease in level of repolarisation such that threshold for an AP is reached more quickly. The frequency of APs is increased increasing the heart rate (**tachycardia**) and thus the cardiac output.
    - **Sympathetic neurons** also increase conduction velocity by decreasing the AV nodal delay. This decreases the duration of systole which is critical as heart rate increases because filling can only occur during diastole.
    - **Parasympathetic neurons** to the SA node conversely decrease the AP frequency and suppress the opening of funny and T-type Ca^{++} channels, decreasing the slope of spontaneous depolarisation and causing a hyperpolarisation such that threshold is reached more slowly. The frequency of APs is thus decreased decreasing the heart rate (**bradycardia**) and thus cardiac output.
    - **Parasympathetic neurons** also decrease conduction velocity by increasing AV nodal delay. This increases the duration of systole.
2. **Hormonal control**
    - The **adrenal medulla** secretes adrenaline which increases AP frequency at the SA node and thus heart rate. It also increases AP conduction velocity.
    - Because increased sympathetic nervous activity is coupled with enhanced adrenaline secretion, the hormone's actions generally reinforce the effects of sympathetic neural input.

5.4 Understand the concept of myocardial contractility, how it may be altered and its effect on cardiac output

- Myocardial contractility or **inotropy** is the change in contractile force **independent** of preload or the **capacity** of the ventricle to **generate force**. Increased contractility implies higher contractile velocity and increased SV and hence **cardiac output**. Positive inotropy is defined as increased contractility whilst negative inotropy is reduced.

5.4.1 Positive inotropy

Positive inotropy is induced by many factors:



1. **Anrep effect**: Increased afterload increases inotropy indirectly. Sustained tension activates Na^+/H^+ exchangers resulting in Na^+ influx. This decreases the Na^+ gradient exploited by the Na^+/Ca^{++} exchanger resulting in intracellular Ca^{++} accumulation.
2. **Drugs**
3. **Sympathetic nerves**: The sympathetic nervous system increases inotropy **indirectly** via the **Bowditch effect** as well as **directly** by releasing **noradrenaline**. The Bowditch effect results in the accumulation of Ca^{++}. It occurs because at higher heart rates, the Na^+/K^+-ATPase which removes Na^+ brought into the cell by the Na^+/Ca^{++} exchanger cannot keep up with the rate of Na^+ influx. Since the driving force behind Ca^{++} transport is the Na^+ gradient, the transport becomes less efficient resulting in an accumulation of Ca^{++} inside the cell.

   Noradrenaline binds to β_1 adrenergic receptors, activating the cAMP second messenger system. The cAMP then activates protein kinases that result in,

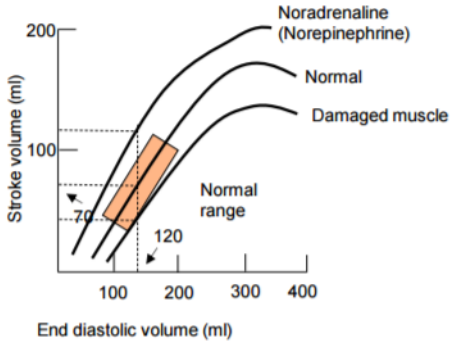
   (a) **Augmentation** of open state of Ca^{++} channel, increasing Ca^{++} influx.
   (b) **Enhanced** release of Ca^{++} from the SR.
   (c) **Increase** crossbridge cycling by increasing rate of myosin ATPase.
   (d) **Enhanced** rate of Ca^{++}-ATPase activity on the SR, increasing rate of Ca^{++} reuptake and thus the rate of relaxation. This results in faster, stronger contractions.
4. **Directly secreted adrenaline**: Increase stroke volume via the same mechanisms as noradrenaline.

5.4.2 Negative inotropy

Negative inotropy is mostly induced by cardiac drugs such as β blockers, Ca^{2+} channel blockers or anaesthetics. There is **negligible** parasympathetic influence on **ventricular contractility** because of sparse ventricular distribution of parasympathetic fibres.

5.4.3 Myocardial contractility and the Frank-Starling relationship

From the previous page, we know that SV increases with contractility. Hence increased contractility shifts the Starling curve upwards **increasing ejection fraction** and vice versa.



6 Lecture 6

6.1 Know Poiseuille's Law and what it describes

Poiseuille's Law gives the **pressure drop** in an incompressible, Newtonian fluid in laminar flow flowing through a long cylindrical pipe of constant cross section.

$$\Delta P = \frac{8\eta LQ}{\pi R^4}$$

- ΔP = pressure difference between two ends
- L = pipe length
- η = viscosity
- Q = volumetric flow rate
- R = radius

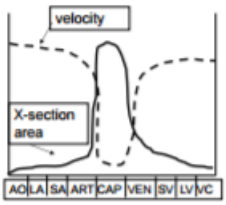
6.2 Understand the relationship between blood flow velocity and cross-sectional area in different sections of the vascular system

Reiterating 2.3, because

$$v = \frac{Q}{A}$$

where A is the **total cross-sectional area of a certain type of vessel**, the velocity is inversely proportional to cross sectional area.

Total cross-sectional area (cm^2)	
Aorta	2.5
Arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Veins	80
Venae cavae	8



Hence, although the capillaries have the smallest individual diameters, they are the most numerous and thus their total across sectional area is the largest. This means the velocity of blood flow through these vessels is the smallest. In general the velocity is higher in vessels with a large cross sectional area relative to radius.

6.3 Understand the concept of resistance to blood flow and the structure and arrangement of blood vessels to counter it

Combining Ohm's and Poiseulle's law,

$$R = \frac{\Delta P}{Q} = \frac{8\eta L}{\pi R^4}$$

Series circuit: $R_t = \sum_{i=1}^{n} R_i \Rightarrow$ Separate elements arranged in series (artery, arteriole etc).
Parallel circuit: $\frac{1}{R_t} = \sum_{i=1}^{n} \frac{1}{R_i} \Rightarrow$ Similar elements arranged in parallel.

6.3.1 Total Peripheral Resistance

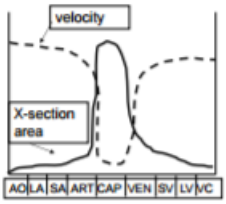
From Ohm's law,

$$MAP = CO \times TPR$$

For an average MAP of 100 mmHg and CO of 5000 ml/min, TPR = 0.02 mm/Hg/ml/min or PRU.

6.3.2 Arterioles Resistance vessels

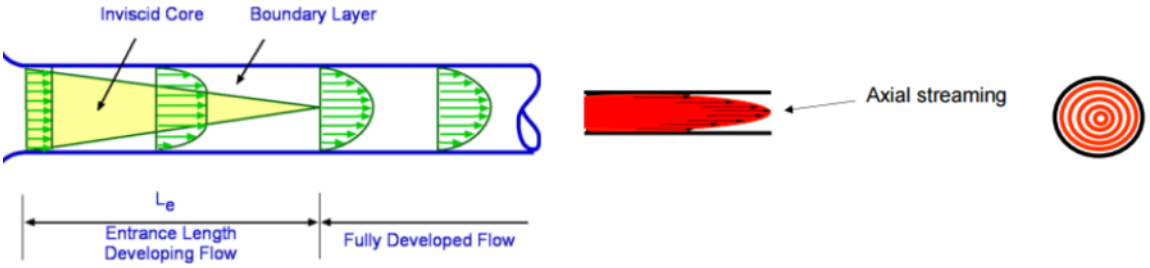
Total cross-sectional area (cm^2)	
Aorta	2.5
Arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Veins	80
Venae cavae	8



The resistance to flow is highest in the arterioles because the number of arterioles is insufficient to compensate for their small diameter. Nervous input also causes their constriction.

6.4 Appreciate the concepts of laminar and turbulent blood flow

- **Laminar flow** takes the form of a **parabolic velocity profile** and can be visualised as a series of cylindrical layers. At the entrance, as the flow begins to develop, because of the viscous drag imparted by the walls, the outermost layer travels the slowest (the velocity at the wall is 0 due to the no-slip effect), whilst the velocity increases as the distance from the wall approaches the radius because the effect of viscous drag decreases. The higher the flow velocity, the larger the viscous drag imparted by the walls, resulting in **axial streaming**.



- Irregular fluid motions within vessel cause **turbulent flow**. Greater pressure is required to force turbulent flow through a tube because, $Q_{laminar} \propto \Delta P$, whilst $Q_{turbulent} \propto \sqrt{\Delta P}$.

6.4.1 Reynold's Number

$$Re = \frac{\rho V D}{\eta}$$

- $Re \leq 2300 \Rightarrow$ Laminar
- $2300 \leq Re \leq 4000 \Rightarrow$ Transitional
- $Re \geq 4000 \Rightarrow$ Turbulent

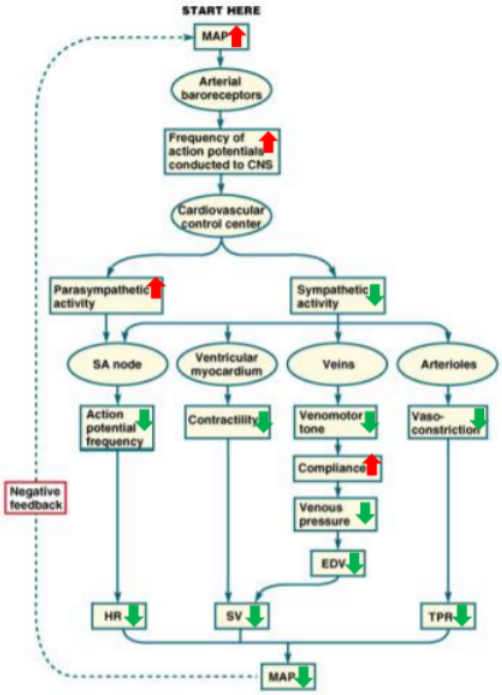
7 Lecture 7

7.1 Understand the role of the autonomic nervous system in controlling the cardiovascular system

- **Blood pressure** requires careful maintenence and blood flow needs to be directed to where it is needed. This flow is mainly controlled by the **ANS**. The ANS takes sensory inputs via various receptors and effects a sympathetic or parasympathetic response via the motor neurons. Because parasympathetic neurons only innervate the atria, the sympathetic nerves are more heavily involved in cardiovascular control. The main effect of sympathetic activity is partial construction to maintain pressure (vasomotor tone).
- In summary, sympathetic nerve stimulation,
  1. **Constricts arterioles**, increasing resistance and blood pressure. It does not constrict capillaries because they have on smooth muscle.
  2. **Constricts veins**, increasing venous return and cardiac output.
  3. **Increases heart rate** and **inotropy** increasing cardiac output and blood pressure.
- The **medulla oblongata** is the main cardiovascular control area. The **cardioinhibitor centre** is the origin of the parasympathetic nerves .e.g. the vagus. Sensory inputs from receptors input into the **vasodilator area** which directly stimulate the cardioinhibitor centre. The origin of the sensory nerves is the **vasocontrictor centre**.
- The only diference between noradenaline and adrenaline is that adrenaline causes vasodilation of arteries in muscle.

7.2 Know the mechanism of the baroreceptor reflex in controlling blood pressure

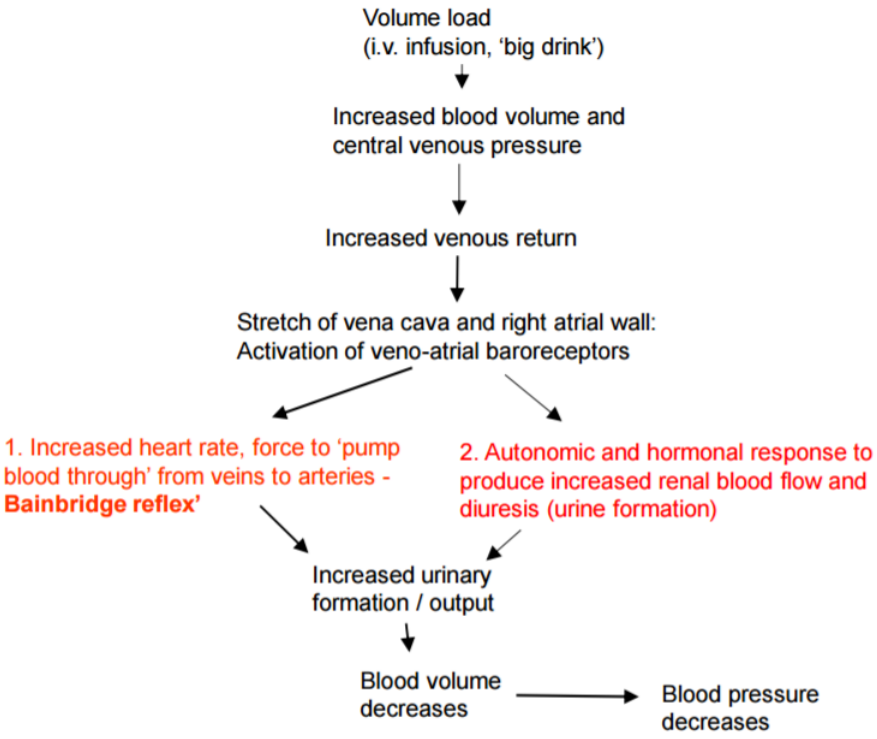
Short-term control of blood pressure is controlled via a **negative feedback loop** using baroreceptors in the **aortic arch** and **carotid sinuses**. Baroreceptors sense pulsatile and static pressure. Baroreceptors are tonically active and constantly firing APs at a certain rate. Increasing BP stimulates them to fire at a higher rate to decrease BP, whilst falling BP stimulates them to fire at a lower rate to increase BP.



1. A high MAP activates arterial baroreceptors to increase the frequency of APs conducted to the cardiovascular control area.
2. This results in an increase in parasympathetic activity in the SA node, decreasing AP frequency in pacemaker cells and decreasing HR.
3. Furthermore there is an increase in sympathetic activity which results in three things:
   (a) Decreases ventricular contractility decreasing SV.
   (b) Decreases venomotor tone incresing compliance and decreasing venous pressure decreasing venous return and thus EDV. Ultimately decreases SV.
   (c) Decreases construction of arterioles, decreasing TPR and thus MAP.

7.3 Appreciate the role of low-pressure baroreceptors in blood pressure maintenance

Low pressure baroreceptors located in the vena cavae and right atrium are activated by an increase in blood voume and act to decrease blood volume and **blood pressure** by increasing water loss through the kidney via the **volume reflex**.



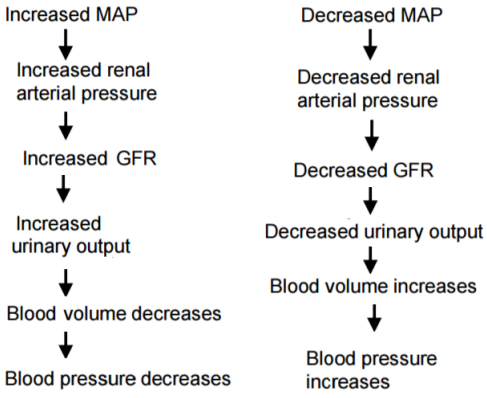
The reason for their location is because changes in volume acutely affect the venous volume because they are the capacitance vessels. They also have inputs into the hypothalmus concerned with controlling blood volume and osmolarity.

7.4 Understand that long-term maintenance of blood pressure involves regulation of blood volume, and the kidneys are vital in this role

Long-term increases in blood pressure are opposed by a reduction in blood volume, through **diuresis** and **natriuresis**. Additionally the **renin-angiotensin-aldosterone** system acts to increase blood volume and peripheral resistance should blood pressure fall.

7.4.1 Pressure diuresis and natriuresis

- **Natriuresis** is the excretion of Na^+ (addressed in 7.4.2). **Diuresis** is the formation of urine.
- Changes in MAP alone cause changes in urinary output (water and Na^+) via the mechanisms below.



7.4.2 Natriuresis

- 2/3rds of the body's water is intracellular and only a 1/3rd is extracellular. Conversely, $[Na^+]_{ec} >> [Na^+]_{ic}$ because the Na^+-K^+-ATPase is constantly pumping Na^+ into the extracellular fluid. If you eat a lot of salt, Na^+ accumulates extracellularly, exerting an osmotic pressure and drawing water out of the cells, increasing blood volume and thus pressure.
- Na^+ can be excreted by **increasing water intake**.

7.4.3 ADH (Vasopresin)

- The hypothalmus produces and releases **antidiuretic hormone (ADH)** also known as **vasopresin**, via the **pituitary gland**.
- Its release is induced by dehydration/decreased blood volume and acts to reabsorb water to **concentrate urine** and **vasoconstrict** to increase MAP.

7.4.4 Renin-angiotensin-aldosterone system (RAAS)

- **Low GFR/BP** stimulates the sympathetic nervous system to produce **renin**.
- **Renin** converts **angiotensinogen** from the liver to **angiotensin I**.
- **ACE** converts **angiotensin I** to **angiotensin II**.
- **Angiotensin II** has 2 main effects:
  1. Causes **vasoconstriction** increasing **TPR**
  2. Causes increased Na^+ reabsorption increasing blood volume and thus MAP.
  3. Causes **aldosterone** secretion which increases Na^+ reabsorption increasing blood volume and thus MAP.

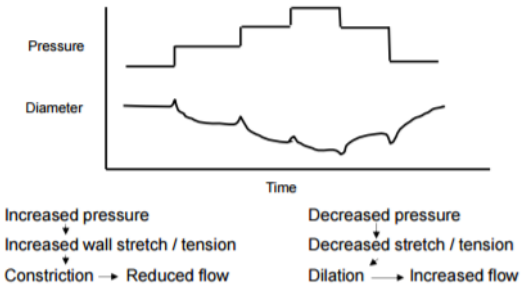
8 Lecture 8

8.1 Understand the concept of autoregulation of blood flow and the main theories developed to explain it: myogenic, metabolic and endothelium-dependent regulation

Autoregulation ensures **stable bloodflow** in the face of fluctuations in pressure. **3 theories** have been formulated to explain its mechanism.

8.1.1 Myogenic theory

- The smooth muscle in (**arterioles**) constrict and dilate in response to changes in **intra-luminal pressure** and thus tension of the walls. This is a **myogenic response** because it is independent of endothelium/neurohormonal factors.



8.1.2 Metabolic theory

Metabolic theory refers to the local regulation of arterial vasomotion based on the metabolic needs to the surrounding cells. There are two major theories of the mechanism.

1. **Oxygen lack theory**:
   - Oxygen (as well as other nutrients) is needed to cause vascular smooth muscle contraction. At rest the arterioles are normally kept partially constricted. In the absence of adequate O_2, the muscles can't remain contracted and relax causing vasodilation.
2. **Vasodilator formation**
   - Blood vessels can also respond to **ischaemia**; a generalised decrease in flow and hence nutrients rather than a specific lack of O_2. This response is called **hyperemia**.
   - **Active hyperemia** is when increased activity results in a **higher metabolic rate**, increasing O_2 consumption, CO_2 production and causes the build up of other **metabolites**. This causes the **local arteriolar smooth muscle** to relax causing **vasodilation** decreasing resistance and increasing blood flow to compensate.
   - **Reactive hyperemia** is exactly the same except it is triggered by a **decrease/increase in blood flow** possibly due to occlusion rather than metabolic need. The argument for reactive hyperemia being related to **metabolite accumulation** is based on the observation that the **extent of rebound flow** following **occlusion** increases with the **time of occlusion**. The longer the occlusion the greater the accumulation of metabolites causing a larger extent of **vasodilation**.
   - Some of the substances that mediate this vasodilation are:
     (a) **Adenosine**: vasodilator in coronary arteries/skeletal vessels
     (b) CO_2: increases H^+ concentration via the carbonic acid equilibrium lowering pH causing vasodilation.

(c) K^+: released by active skeletal/cardiac muscle. Extracellular K^+ increases with AP frequency because with each AP, K^+ leaves the cell. Normally the Na^+-K^+-ATPase can restore the ionic gradients, but the pump cannot keep up with the rapid depolarisations (there is a time lag) during contractions causing K^+ to accumulate extracellularly. This results in hyperpolarisation of the vascular smooth muscle resulting in vasodilation.

(d) **Histamine**: (see next dotpoint)

(e) **Prostacyclin**: Released by endothelial cells causing vasodilation.

3. **Endothelium dependent regulation**

- Increased flow imparts more shear force stimulating release of NO relaxing smooth muscle and causing vasodilation.

8.2 Appreciate the role of several hormones (angiotensin II, bradykinin, histamine) in controlling systemic and local blood flow

- **Adrenaline**: Dilates skeletal muscle, coronary arterioles. Constricts others.
- **Noradrenaline**: Vasoconstriction.
- **Angiotensin II**: Vasoconstrictor. Acts systemtically.
- **Endothelin**: Vasoconstructor.
- **Bradykinin**: Vasodilation. Increases capillary permeability allowing more immunoglobulins to get out of plasma and combat inflammation. Short half-life, inactivated by ACE.
- **Histamine**: Vasodilation. Increases capillary permeability. Released during allergic responses (for the same purpose as bradykinin).

8.3 Understand the main mechanisms modulating blood flow in the skin, heart, skeletal muscle, lungs and brain

1. **Cutaneous circulation**: Controlled mainly by sympathetic nerve activity
2. **Coronary/Skeletal muscle**: Blood flow in the coronary and skeletal muscle circulations is determined by the mechanical effects of compression (systole) and distension (diastole) and metabolic hyperemia, mediated primarily by adenosine in the coronary circulation. Adrenaline is an important vasodilator in skeletal muscle.
3. **Pulmonary blood flow**: Matched to oxygen saturation surrounding alveoli. Hypoxia causes pulmonary vasoconstriction (no point letting blood through of there's no O_2 coming in. Maintains ventilation perfusion ratio $\frac{V}{Q}$), mediated by endothelial secretions.
4. **Cerebral bloodflow**: Not moderated by sympathetic nervous activity but relies on local metabolites, mainly CO_2 and K^+.

9 Lecture 9

9.1 Understand the roles of arterioles, capillaries and venules in the microcirculation

- **Arterioles** are the **resistance** vessels that control blood flow into capillaries through their contractile state.
- **Capillaries** are the **exchange** vessels that control nutrient/waste exchange.
  - **Continuous**: Regular intracellular gaps. In most tissue.
  - **Fenestrated**: Large pores. Found in areas where lots of filtration is required.
  - **Discontinuous**: Found in spleen/liver/bone marrow where proteins and cells must cross endothelium. Very large gaps.
  - **Blood brain barrier**: Endothelium has no holes at all. Protects brain from waterborne toxins.
- **Venules** are capacitance vessels. See 5.2 for more info.

9.2 Appreciate the mechanisms of substance exchange at the capillary level: diffusion, filtration and pinocytosis

9.2.1 Diffusion

- Diffusion is responsible for 98% of trans-capillary exchange.
- It is dictated by Fick's Law,
$$J = -PS(C_o - C_i)$$
  - P = permeability to substance
  - S = capillary surface area
  - $C_o - C_i$ = concentration gradient
- Capillaries are **highly permeable** to lipid-soluble substances/gases. They are **moderately permeable** to small charged particles, but are **poorly permeable** to large charged particles (.e.g. proteins).

9.2.2 Pinocytosis

- Movement of large lipid-insoluble molecules into the cell by enclosing them in a vesicle made of plasma membrane. The plasma membrane invaginates a target particle, forming a pocket around it. The pocket then pinches off with the help of specialised proteins leaving the particle trapped in a vesicle of vacuole inside the cell.Important towards venous end of capillaries/muscle. Less important in lung/brain.

9.2.3 Filtration (See next dotpoint)

9.3 Understand the Starling forces and equation controlling and balancing the net movement of fluid in and out of capillaries

- Four 'Starling' pressures collectively determine the rate and direction of water passage through capillary fenestrations.
  1. **Hydrostatic pressure** of blood P_c moving fluid out of capillary.
  2. **Hydrostatic pressure** of interstitial fluid P_{if} moving fluid into capillary.
  3. **Colloid osmotic pressure** π_p of plasma proteins in blood moving fluid into capillary.
  4. **Interstitial colloid osmotic pressure** π_{if} of plasma proteins in interstitial fluid moving fluid out of capillary.
- Defining efflux as positive, summing the pressures, letting $k = PS$ and using Fick's Law yields **Starling's Equation**,
$$J_v = k[(P_c + \pi_{if}) - (P_{if} + \pi_p)]$$

- We define the **net filtration pressure** as $NFR = (P_c + \pi_{if}) - (P_{if} + \pi_p)$
- The average values of the Starling pressures are listed below for both the arterial and venous ends.

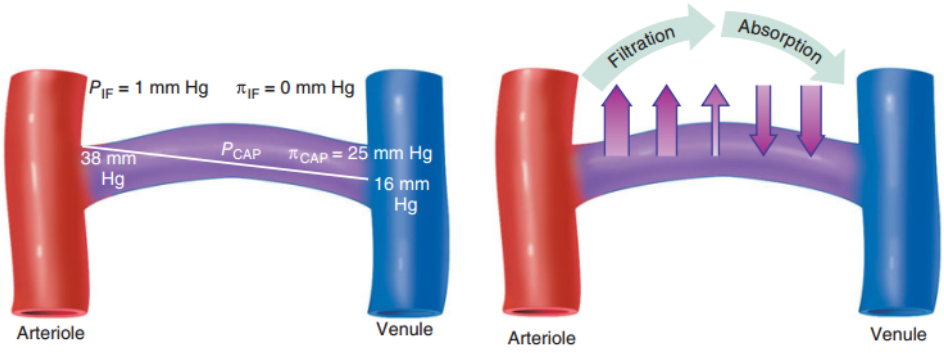
Arteriole end

- $P_c = 38$ mmHg, $\pi_{if} = 0$ mmHg, $P_{if} = 1$ mmHg, $\pi_c = 25$ mmHg

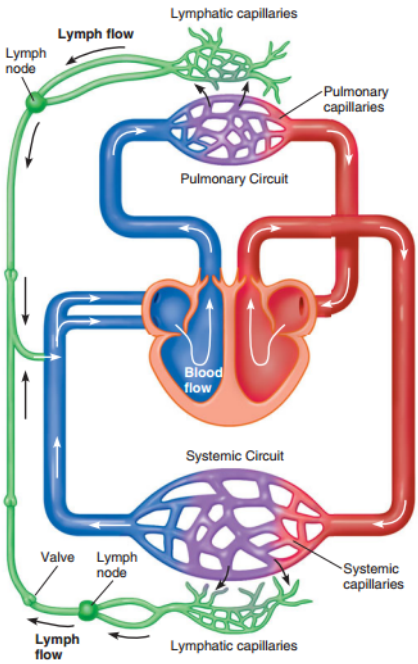
Venule end

- $P_c = 16$ mmHg, $\pi_{if} = 0$ mmHg, $P_{if} = 1$ mmHg, $\pi_c = 25$ mmHg
- If we calculate the NFR for both ends,

$$NFR_{arteriole} = 12\,\text{mmHg} \qquad NFR_{venule} = -10\,\text{mmHg}$$

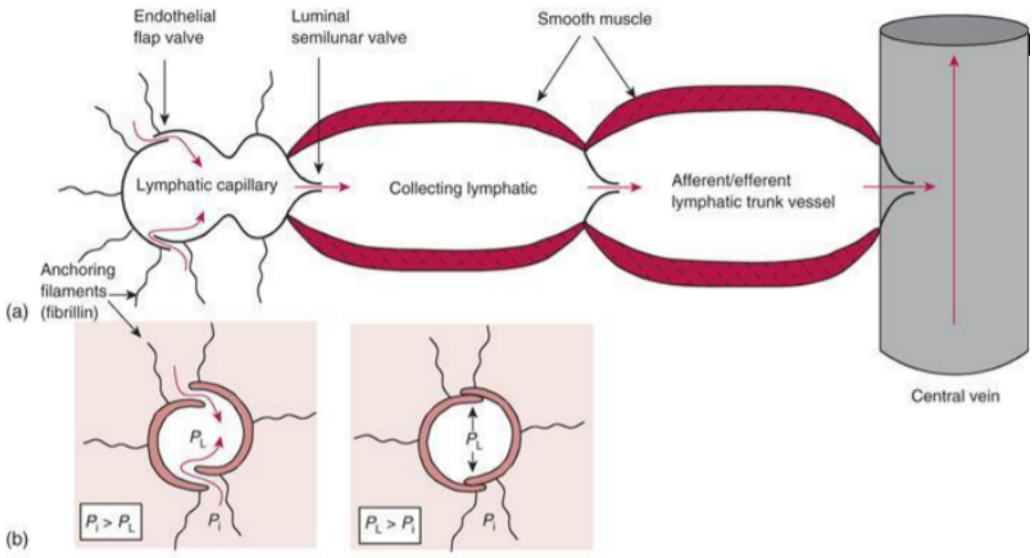


- this means that most of the filtration occurs at the **arteriolar end** whilst the absorption occurs at the **venular end**.
- If we take the same values of π_{if}, P_{if}, π_c, but take the mean P_c and recalculate the NFR, $\Rightarrow NFR = 2$ mmHg. This tells us that there is a **net leakage of fluid** escaping from the capillaries over time. This leakage drains into the **lymphatic system**.

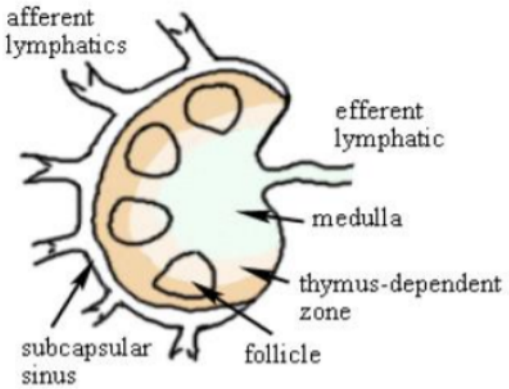


9.4 Appreciate the role of the lymphatic system in retrieving tissue fluid

- The **lymphatic vessels** are closed-end and highly permeable.
- Although lymph fluid has less protein than plasma, the **large gaps** between the endothelial cells of lymphatic vessels allow the reabsorption of protein from the fluid(capillaries cannot do this).
- Lymphatic vessels are anchored to surrounding walls by filaments.
    1. If the interstitial pressure P_i is higher than the lymphatic pressure P_L, the lymph fluid pushes the wall apart, creating a negative pressure that draws the fluid in.
    2. When $P_L > P_i$ the gaps are sealed.
    3. Once the fluid enters the lymphatic capillaries, smooth muscle contracts raising the pressure in the vessel which pushes the valves in each segment as the fluid travel through.



- Anything increasing filtration will increase lymph formation. Blocking lymphatics can lead to **lymphatic oedema** or **lymphoedema**.
- **Lymph nodes** are responsible for **immune surveillance**. Lymph enters the node through the afferent lymphatics, is filtered through the follicle and then leaves the node via efferent lymphatics.

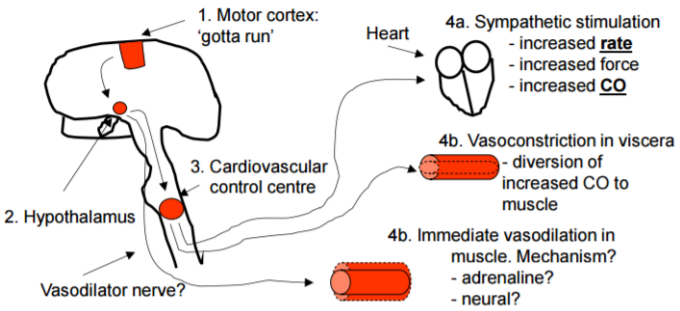


9.5 Understand the integrated cardiovascular response to exercise

- During **exercise** cardiac output is altered according to the table in **1.7**.
- The cardiovascular response to exercise consists of **early** and **delayed** components.

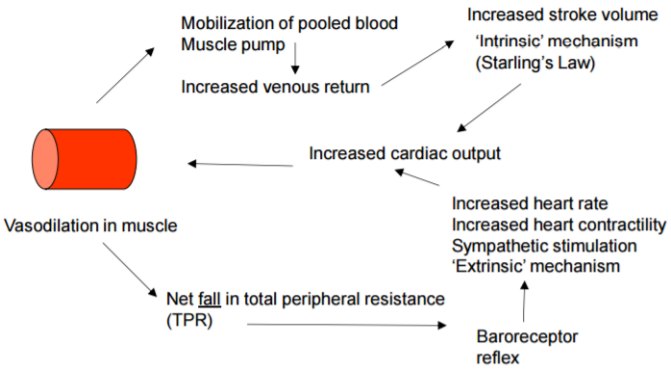
Early integrated response

- The early integrated response is initiated by the CNS.
  1. Motor cortex signals the cardiovascular control centres in the upper medulla via the hypothalmus that stimulate rapid early onset sympathetic nerve stimulation.
  2. This stimulation increases CO by increasing heart rate and inotropy.
  3. Vasoconstriction in viscera so that CO can be diverted to the active nuscles.
  4. Immediate vasodilation in muscle. Mechanism is still debated.



Delayed integrated response

1. **Metabolic dilation**: Working muscle releases K^+ and other metabolites (adenosine, lactate, $CO_2 \Rightarrow$ decreased pH) causing **vasodilation** resulting in increased flow and capillary recruitment.
2. **Sustained increase in cardiac output**



3. **Other factors**
   - **Local histamine release**: Vasodilation. Increased capillary permeability $\Rightarrow$ increased lymph flow.
   - **Adrenaline release**: Increased CO via dilation of coronary/skeletal vessels.
   - **Stretch receptors in muscle (myogenic)**: reflex activation of CV centre.
   - **Temperature increase**: Vasodilation of skin vessels/sympathetic stimulation of sweat glands (non apical).