Lecture 26: Cardiovascular System

- Arteries travel away from the heart.
- Veins travel to the heart (regardless of degree of oxygenation).
- Cardiac output (5L/min) is distributed throughout the organs.
- Oxygenation occurs in the lungs.
- A red blood cell will run through vascular beds in series but not through beds running in parallel.
- Note capillary beds in series in the kidneys: filtration/reabsorption

The flow of blood is driven by a pressure gradient.

Pressure gradient \((\Delta P) = P_1 - P_2 = QR\)

where \(R\) is the resistance to flow

Blood only flows if there is a positive pressure gradient
**Factors affecting resistance:**
- $R = kl/r^4$
- Length of vessel.
- Radius of vessel.
- Viscosity of the blood.
**Resistance of a network of blood vessels:**
- **Series:**
  - $R_{\text{Total}} = R_1 + R_2 + R_3$
- **Parallel:**
  - $1/R_{\text{Total}} = 1/R_1 + 1/R_2 + 1/R_3$
- The arterial and venous systems offer relatively little resistance to flow.
- The arteriolar system as a whole has a relatively high resistance (60-70% of the total resistance of the entire circulation).
- The capillary system as a whole has a resistance, which is less than that of the arteriolar system, even though capillaries have the narrowest internal diameter of all blood vessels.
**Cardiac output and total peripheral resistance:**
- For a system of vessels, Ohm’s law also applies:
  - Pressure gradient ($\Delta P$) = $Q R$
- In the case of the entire systemic circulation,
  - $\Delta P = \text{mean arterial pressure (MAP)} - \text{right atrial pressure (RAP)}$
  - $Q = \text{total flow through the systemic circulation = cardiac output (CO)}$
  - $R = \text{total resistance of the systemic circulation, referred to as the total peripheral resistance (TPR)}$
- Thus, for the entire systemic circulation, $\Delta P = \text{MAP - RAP = CO x TPR}$
- But RAP ~ 0 mmHg, therefore (to a good approximation):
- For a system of vessels, Ohm’s law also applies:
  - Pressure gradient ($\Delta P$) = $Q R$
  - $\text{MAP = CO x TPR}$
  - Cardiac output = stroke volume x heart rate
  - Mean pulmonary arterial pressure is ~1/3 that of MAP, and therefore pulmonary vascular resistance is also ~1/3 that of TPR.
**Slow blood flow velocity through capillaries:**
- Velocity ($V$) = Flow ($Q$)/Cross-sectional Area ($A$)
**Blood pressure and blood flow velocity at different sites in the systemic circulation:**
- The largest pressure drop is across the arterioles.
- Pressure drop along arteries is minimal; therefore arterial pressure can be estimated at any site in the arterial tree.
- Right atrial and central venous pressure is close to zero.
- The blood flow velocity in the capillaries is minimal, approximately 1/1000 that in the aorta
- The elastic properties of a blood vessel can be measured by determining the relationship between the static pressure and volume of a segment of that vessel.
- This is called the capacitance (or sometimes compliance).
- Compliance ($C$) = $\Delta V/\Delta P$ where $\Delta V$ is the change in volume, and $\Delta P$ the corresponding change in pressure.
- Venous capacitance is about 20 times arterial capacitance (walls of veins are more distensible).
- That is why an increase or decrease in total blood volume is taken up into, or lost from, the venous system.
**Factors affecting arteriolar diameter (and therefore vascular resistance):**
- Local factors: myogenic activity, metabolites, histamine, heat/cold
- Autonomic nerves: sympathetic vasoconstrictor nerves (nearly all beds), parasympathetic vasodilator nerves (some beds)
- Circulating hormones: adrenaline (epinephrine), noradrenaline (norepinephrine), vasopressin, angiotensin II
Summary:
- Blood leaves the left side of the heart under high pressure entering the arteries => arterioles => capillaries => venules => veins and returns to the right side of the heart. This is the systemic circulation.
- Cardiac output is distributed throughout the body.
- Capillary beds may be in series or parallel.
- Blood leaves the right side of the heart under a lower pressure (~ 1/3 that of the systemic circulation) to become oxygenated in the lungs (pulmonary circulation).
- Blood flows when there is a pressure gradient: delta P = Flow x R (resistance)
- Mean Arterial Pressure = Cardiac output x Total Peripheral Resistance.
- Arterioles are the resistance vessels.
- Veins are the capacitance vessels – they hold about 60% of the blood.
- Resistance is dependent on length, viscosity and radius.
- \( R = k l / r^4 \) (Poiseuille’s Law)
- Resistance in series increases total resistance. Resistance in parallel reduces total resistance. The higher the resistance the greater the pressure drop across it.
- Vasoconstriction or dilation occurs when smooth muscle in the vessel wall contracts or relaxes. Contraction causes constriction, which increases resistances and decreases flow (and vice versa).
- The production of local metabolites has powerful effects on arteriolar radius - Adenosine, H+, NO, K+, CO2 accumulation induce local vasodilation.
- The sympathetic nervous system can stimulate vasoconstriction through alpha 1 receptors.
- Adrenaline can induce vasodilation in beds with beta 2 receptors.
- Velocity of blood = flow/cross sectional area.
- Velocity is slowest in the capillaries as the area covered by the capillaries is largest.
- Veins are compliant – a reasonable change in volume only produces a small change in pressure (this is not the case in the arteries).

**Lecture 27: Cardiovascular System II**

- Blood enters the right atrium through the superior and inferior vena cava; the atrium swells as blood enters.
- Upon contraction blood is pushed from the right atrium into the right ventricle through the tricuspid valve.
- After the contraction of the atriums, the ventricles contract forcing blood through the pulmonary semilunar valve into the pulmonary arteries that take blood to the left and right lungs. This is deoxygenated blood that has been returned to the heart from the systemic system.
- The blood is oxygenated in the lungs and returns to the heart through the pulmonary vein, filling the left atrium.
- The atrium swells with blood and contracts, pushing blood through the **bicuspide valve** and into the left ventricle.
- The **ventricles contract** and blood is forced out of the heart through the **aortic semilunar valve** and into the aorta.
- The left ventricle has a thick, muscular wall as this ventricle pushes blood to the entire body at a much higher pressure than blood travelling through the pulmonary system.
- The blood pressure in the pulmonary system is about 20% that in the systemic system.

- Isovolumetric contraction is the contraction of the ventricles after they have filled with blood.
- Before the ventricles contract, the blood pressure is **diastolic**.
- After the ventricles contract, the blood pressure is **systolic**.
- As pressure in the ventricles falls, the pressure in the aorta is high and the aortic valve prevents blood from flowing back into the ventricle.
- Every time there is a pressure difference, a valve will open or shut.
• An ECG detects the current running through the heart muscle.
• These currents are either depolarising or repolarising.
• ECG is measurement of the hearts electrical signals.
• Each peak and trough represents a depolarisation and a repolarisation of different muscles within the heart.
• **P Wave**: Depolarisation of atrial myocardium. Precedes onset of atrial contraction.
• **T Wave**: Repolarisation of ventricles. Beginning of ventricular relaxation.
• **Definitions**:
  - **Systole**: contraction
  - **Diastole**: relaxation
  - **Stroke volume (SV)**: volume of blood ejected by the left ventricle in one cardiac cycle
  - **End-diastolic ventricular volume (EDV)**: volume of blood in the ventricle at the end of ventricular diastole
  - **End-systolic ventricular volume (ESV)**: volume of blood in the ventricle at the end of ventricular systole
  - **Ejection fraction**: ratio of stroke volume to end-diastolic ventricular volume (normally 50-70%)
  - **Atrial pressure** is normally low (close to zero)
  - **Ventricular pressure** varies greatly during each cardiac cycle.
  - **Peak pressures** in the right ventricle and pulmonary artery is much less (about 1/3) than peak pressures in the left ventricle and aorta.
• **Work of the heart**:
  - The work done by the heart in pumping blood from the ventricle into the aorta during a cardiac cycle is dependent on 2 factors:
    - (1) The stroke volume (volume work)
    - (2) The pressure against which the left ventricle pumps (pressure work).
  - Work = SV x P
  - The work of the heart is increased during exercise (when stroke volume increases) and also in people with high blood pressure (because of increased arterial pressure).
• **Cardiac Muscle**:
  - **Myocardium** (cardiac muscle):
    - Main constituent of the heart.
    - Also pacemaker cells.
    - Contraction triggered by depolarization of the membrane (an action potential, AP).
    - Coordinated so ventricular fibres contract virtually simultaneously (pumps effectively).
  - **Low-resistance junctions** (intercalated discs) between muscle fibres (allow AP to pass).
  - **Specialized conducting muscle fibres** (facilitate rapid & co-ordinated spread of excitation).
• **Summary:**
  - Blood returns to the heart through the vena cava into the right atrium through the AV valve and into the ventricle.
  - The right side of the heart pumps to the lungs (pulmonary circulation) and the left side to the body (systemic circulation).
  - The AV (atrio-ventricular) valves prevent the backflow of blood into the atrium (when the ventricle contracts).
  - The pulmonary and aortic valves prevent backflow of blood into the ventricles (from the lungs or the aorta) when the ventricles relax.
  - The valves ensure blood travels through the heart in one direction.
  - The valves open and close in response to the pressure differential across the valve.
  - The cardiac cycle consists of phases of ventricular filling, atrial contraction, isovolumetric (same volume) ventricular contraction, ventricular ejection, and isovolumetric ventricular relaxation.
  - Isovolumetric phases occur when both sets of valves are closed (therefore the volume in the ventricle cannot change).
  - The volume of blood in the ventricle at the end of filling as the ventricle contracts and the AV valve closes is called the end-diastolic volume (EDV).
  - The volume of blood left in the ventricle after the ejection phase is called the end-systolic volume (ESV).
  - The difference between the EDV and the ESV is the stroke volume – the volume ejected with the ventricular contraction – and this is a fraction of the EDV (the ejection fraction).
  - Aortic pressure traces have a maximum of systolic pressure and a minimum of diastolic pressure. Note that the aortic pressure remains high during ventricular relaxation (diastole) compared to the ventricular pressure trace.
  - Large changes in pressure occur in the left ventricle. Atrial pressure changes are small by comparison.
  - The ECG has three distinctive waveforms: P (atrial depolarization), QRS (ventricular depolarization & atrial repolarization) and T (ventricular repolarization). The ECG is seen when the current runs through the muscle mass (not when the current is being conducted through the conduction system).
  - The two heart sounds S1 and S2: lub-dub are associated with the closing of the AV and aortic/pulmonary valves respectively. S1 occurs just after the QRS and S2 just after the T wave.
  - Remember the electrical events precede the mechanical.

**Lecture 28: Cardiovascular System III**

- 3 types of cardiac cells:
  - 1. Pacemaker cells (generating APs in a rhythmic fashion)
  - 2. Specialized conducting fibres
  - 3. Normal contracting myocardial fibres (Atrial and Ventricular)
- **Heart Beat:**
  - Cardiac muscle cells of the heart muscle contract spontaneously due to action potentials.
  - The action potentials begin in the right atrium and originate at the sinoatrial node, radiating out to the left atrium, stimulating the contraction of the atria, before travelling to the atrioventricular node.
  - The action potentials pass slowly through the atrioventricular node into the interventricular septum.
  - This action potential travels very quickly and moves to the bottom of the ventricles (apex) through bundle fibres and starts a contraction from the bottom up in both ventricles, through the Bundle of His consisting of Purkinje fibres, which extends to the ventricular walls.
- **Pacemaker potential:**
  - The pacemaker potential gradually becomes less negative until it reaches threshold, triggering an action potential.
Ions move through ‘funny’ channels.

**Autorhythmicity:**
- Most cardiac cells have the capability to generate action potentials in the absence of any external stimulus.
- The sino-atrial (SA) node has this capability to the greatest degree.
- Propagation of APs through the atroventricular node is delayed by approx. 100 msec (fibres of A-V node are narrow & branching = v. slow conduction velocity/long delay).
- Depolarisation of autorhythmic cells rapidly spreads to adjacent contractile cells through gap junctions.

**Phase 0:**
- Inward flow of Na+

**Phase 1:**
- Decreased entry of sodium and potassium, increased entry of calcium.

**Phase 2:**
- Slow inward flow of calcium, slow outward flow of potassium.

**Phase 3:**
- Fast outward movement of potassium.

**Phase 4 Rest Period:**
- Na"-K" pump eliminates excess Na+ that entered during phases 0 and 1 in exchange for K+ that exited during phases 2 and 3.
• **Refractory Period:**
  - Duration of the cardiac contractile response is very similar to that of the cardiac action potential and therefore also to that of the refractory period.
  - Therefore myocardial fibres cannot be re-excited until the action potential is completed.
  - Therefore summation of contractions (tetanus) cannot occur in cardiac muscle.

• **Summary:**
  - Cells in the heart (i) generate APs automatically (ii) conduct the current quickly through the heart or (iii) contract.
  - Pacemaker cells spontaneously depolarize to threshold generating an action potential and a cardiac contraction.
  - Sympathetic stimulation increases the slope of the pacemaker potential and makes the starting point of the potential more positive by changing ion permeability. This increases the heart rate.
  - Parasympathetic control of the heart rate is dominant and decreases heart rate by decreasing the slope of the pacemaker potential and by shifting the starting point of the potential to a more negative value.
  - Movement of ions (both Na and K) through the “funny” channels brings the pacemaker potential towards threshold. Calcium channels open when funny channels close and bring the potential to threshold.
  - Depolarization in pacemaker cells is due to the influx of calcium ions. Repolarization due to the efflux of potassium.
  - The cardiac pacemaker cells (SA node, AV node and purkinje) demonstrate autorhythmicity and can generate a heart rate without an external stimulus. The inherent rates are SA node > AV node > purkinje.
  - Usually conduction is initiated in the SA node, travels through the internodal fibres to the AV node through the bundle of His, left and right branch bundles and the purkinje fibres. The atria and ventricles are electrically isolated from each other – conduction through the AV node only with a ~100msec delay.
  - Cardiac muscle cells are dependent on extracellular calcium for contraction – Calcium-induced calcium release. Extracellular calcium is required for release of calcium from the sarcoplasmic reticulum. Force of contraction is dependent on intracellular calcium concentration.
  - Ventricular muscle action potentials display a long plateau phase 2 (balance of calcium influx and potassium efflux). Depolarization is due to Na influx (not calcium like pacemaker cells). The long duration of the action potentials ~250 msecs prevents tetanic contractions occurring in cardiac muscle cells.

**Lecture 29: Cardiovascular System IV**

• **ECG:**

![ECG Diagram](image-url)
ECG shows the deflection caused by the mean current of the heart.

The ECG shows the electrical events preceding muscular contraction.

- P Wave: Atrial depolarisation
- PR segment: AV nodal delay
- PR Interval: Atrial depolarisation and contraction.
- QRS complex: Ventricular depolarisation and simultaneous repolarisation of atria.
- QT Interval: Single cycle of ventricular depolarization and repolarization.
- T Wave: Ventricular repolarisation
- TP interval: Ventricle relaxation (filling)

**Pre-load and after-load:**

- Pre-load is defined as the tension in the ventricular wall at the end of diastole.
- For practical purposes this is measured as the ventricular end-diastolic pressure.
- The heart muscle is always below optimal length and therefore the greater the stretch, the greater the force of contraction.
- Frank-Starling Law: The greater the filling of the ventricle (i.e. end-diastolic ventricular volume), the greater will be the force of contraction (and hence stroke-volume)
- Consequences of Frank-Starling Law:
  - A change in return of blood to right or left ventricle is immediately followed by a change in output (e.g. on changing posture when venous return suddenly decreases or increases).
  - The cardiac output tends to be maintained in the face of changing aortic pressure (afterload).
- **After-load** is defined as the pressure that the ventricles must overcome to eject blood. This is the aortic pressure at the time the aortic valve opens.

**Effect of change in afterload:**

- Neural and hormonal control of cardiac contractility:
Cardiac contractility is defined as the ability of the heart to contract, at any given end-diastolic ventricular volume.

Activation of cardiac sympathetic nerves, or an increase in circulating adrenaline, increases cardiac contractility (indicated by red arrow).

This effect is due to an increase in intracellular [Ca²⁺] in myocardial fibres.

Activation of cardiac vagal nerves leads to a decrease in myocardial intracellular [Ca²⁺], resulting in a reduced cardiac contractility (indicated by blue arrow).

The force of contraction of the heart therefore depends upon both the end-diastolic ventricular volume and extrinsic factors that affect contractility.

**Beta 1 Receptor:**

Cyclic AMP activates protein kinases, which then phosphorylates:

1. Slow Ca²⁺ channels, promoting entry of more Ca²⁺ from the extracellular space
2. An SR protein that causes the SR to release more Ca²⁺
3. Myosin, which increases the rate of myosin cross bridge cycling.
4. In addition, phosphorylation of the SR calcium uptake pump removes Ca²⁺ more rapidly from the sarcoplasm, thus promoting relaxation.

**Factors which affect venous return:**

The most important factor that determines venous return is the pressure gradient for venous return, i.e. difference in pressure between peripheral veins and right atrium.

Two key factors are:

1. Alternate contraction and relaxation of skeletal muscles.
2. One-way valves preventing backflow.

This is a significant factor increasing venous return during dynamic exercise (e.g. running, cycling).

**Definitions:**

1. Inotropic: affects the contractility of the myocardium. Thus, positive and negative inotropic effects refer to increases or decreases, respectively, in cardiac contractility (e.g. adrenaline +ve, barbiturates –ve)
2. Chronotropic: affects the heart rate. Thus, positive and negative chronotropic effect refers to increases or decreases, respectively, in heart rate (e.g. adrenaline +ve, acetylcholine –ve)

**Summary:**

Cardiac preload = the amount of stretch/tension on the ventricular walls just prior to contraction (or at the end of diastole). This is equivalent to the EDV or end-diastolic ventricular volume.

Cardiac afterload = the amount of force the ventricular muscle has to overcome to eject the blood. This is equivalent to the diastolic pressure, which is the pressure the ventricles must exceed to open the aortic valve and eject the blood.

The Frank-Starling Law of the heart describes the relationship between EDV and SV (Stroke Volume).

As more blood returns to the heart and increases the EDV this stretches the ventricular muscle resulting in more optimally aligned actin and myosin filaments => increasing the force of the subsequent contraction and the stroke volume ejected from the heart.

Contractility relates to the increase or decrease in stroke volume for a given EDV.

- Increased contractility = increased force of contraction for a given EDV = positive inotropic effect
- Decreased contractility = decreased force of contraction for a given EDV = negative inotropic effect
- SNS and adrenaline: positive inotropic effect PNS: negative inotropic effect
- Chronotropic effects relate to an increase or decrease in heart rate.

Increases in contractility and HR occur with Beta 1 receptor stimulation (by noradrenaline/adrenaline) which allows (i) increased calcium influx (ii) increased release of sarcoplasmic calcium (iii) enhanced rate of cross bridge cycling and (iv) increased uptake of calcium => speeding up of muscle relaxation. All this provides a faster and more forceful contraction.

Venous return is aided by the respiratory pump, skeletal muscle pump and decreased resistance. VR determined by pressure gradient between peripheral veins and right atrium.

Cardiac output is distributed amongst the organs/tissue beds and can be redistributed by changes in resistance and accumulation of metabolites.
Alpha 1 receptor activation causes generalized vasoconstriction. Local factors have greatest influence on flow.