The Cardiovascular System

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Overview of the circulation

The purpose of the cardiovascular system is to deliver oxygen (O_2) and nutrients to the metabolising tissues, and carry waste products (e.g. carbon dioxide; CO_2) and heat away. The heart is made up of individual muscle cells called cardiac myocytes arranged in a way that forms a functional syncytium (it acts as one muscle) to allow an electrical signal to spread across the heart in a coordinated way. This coordinated electrical activity leads to the mechanical beat; pressure is generated in the walls of the heart to eject blood from its chambers for delivery via the blood vessels to the lungs and systemic tissues.

Anatomy of the cardiovascular system

Gross anatomy of the heart

The cardiovascular system is functionally two circulations arranged in series; systemic and pulmonary (blood is pumped from one circulation into the other). The heart is structurally and functionally two pumps; the right side pumps blood into the pulmonary circulation to allow oxygenation of the blood in the pulmonary capillaries (see Respiratory System chapter) and returns to the left side of the heart. The left side of the heart pumps blood into the systemic circulation to deliver that oxygenated blood to the tissues, and carry waste products (e.g. CO_2) back to the right side of the heart and thus the pulmonary circulation for excretion (see Figure 1). In a normal, healthy, adult heart there is no direct connection between the two.

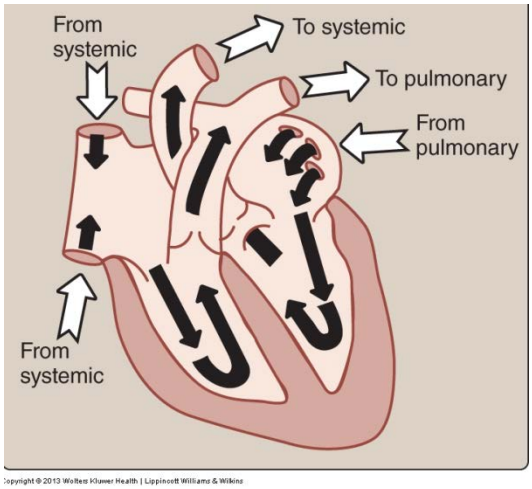

Figure 1 The direction of blood flow through the heart (from Preston & Wilson, Physiology. International Edition ISBN 13-978-1-4511-7567-7)

Chambers

The heart is made up of four chambers; two atria and two ventricles (one of each on each side of the heart). The right ventricle pumps blood via the pulmonary artery into the pulmonary circulation. Oxygenated blood returns from the pulmonary circulation back to the left atrium via the pulmonary vein. Blood from the left atrium drains into the left ventricle down a pressure gradient (see section X), and from there, is ejected into the systemic circulation via the aorta. Oxygenated blood is delivered to systemic tissues via arteries, arterioles and capillaries (see section Structure and function of the blood vessels) and deoxygenated blood returns back the heart via venules and veins, and passively drains into the right atrium via the vena cavae.

Valves

Blood is allowed to flow in one direction through the heart due to strategically placed one-way valves (see Figure 2). Blood flows from the atria into the ventricles via the atrioventricular valves (the tricuspid valve on the right side of the heart and the mitral valve on the left). Blood leaves the ventricles and enters the arterial system via another set of valves; the semilunar valves (the pulmonary valve on the right side of the heart and the aortic valve on the left).

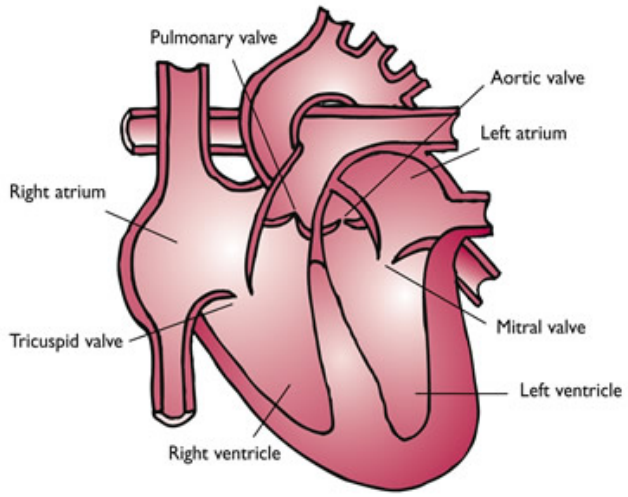

Figure 2 The heart valves (see Figure 1 for direction of blood flow) (from Google images; please redraw)

Structure and function of the blood vessels

The heart generates pressure to help drive the blood around the circulation to deliver oxygen to the tissues, and deliver deoxygenated blood back to the heart. This pressure acts as a unit of energy and thus the pressure is used up, like petrol driving your car from A to B, to move the blood around the circulation. By the time the blood enters the veins to return back to the heart, blood pressure is extremely low.

Blood vessels have some common features, but also some differences which are related to their function. All blood vessels are lined with a single layer of endothelial cells, called the tunica intima. The layer of smooth muscle cells covering the tunica intima in arteries and veins is called the tunica media, and the thin outer layer of

connective tissue in arteries, arterioles and veins is called the tunica adventitia and gives these vessels some stability.

The structure of each of the different class of vessels is related to its function.

Arteries
Arteries deliver lots of blood, very fast and under high pressure to the arterioles. Thus, they are large in diameter, and have lots of elastin and smooth muscle around the walls (see Figure 3). These thick muscular walls help the arteries resist collapse.

Arterioles
Arterioles also have lots of smooth muscle but this smooth muscle is highly innervated by the sympathetic nervous system. Activity in the sympathetic nervous system leads to changes in luminal diameter and hence resistance to blood flow (see section; Regulation of blood pressure; the baroreceptor reflex). This regulates the flow rate downstream into the tissue capillaries (helping to match blood flow, and hence oxygen delivery to the needs of the tissue), and also helps regulate systemic blood pressure upstream (see section; Regulation of blood pressure; the baroreceptor reflex). These vessels are referred to as resistance vessels as they are the main site of vascular resistance to blood flow.

Capillaries
Capillaries are the site of exchange of fluid and blood gases (oxygen and carbon dioxide) between blood and tissues, and as such need to be thin-walled. Thus, they are composed of one layer of endothelial cells (tunica intima) and its basal lamina, with no elastin or smooth muscle. Once blood has passed through the tissue capillaries it becomes venous in nature.

Venules and veins
Venules and veins deliver blood back to the right side of the heart. Venules and veins are thin-walled vessels which have some smooth muscle associated with them. By the time the blood has reached the veins pressure has fallen to very low values, as such one-way valves are needed to help the blood move in one direction back to the heart. The smooth muscles around the walls of the veins are innervated by the sympathetic nervous system. As the diameter of the veins can be quite large, they also act as capacitance vessels, and blood within them is referred to as the venous reservoir (the veins contain approximately 60% of the total blood volume at any one time). This blood can be mobilised in times of emergency such as haemorrhage, by increased activity in the sympathetic nervous system, which decreases the diameter of the lumen and boosts venous return to the heart.

Microcirculation
The microcirculation is collectively the arterioles (the site of resistance to blood flow), the capillaries (the site of exchange between tissue and blood) and post-capillary venules. The microcirculation is responsible for regulating blood flow to tissues, blood pressure and tissue fluid.

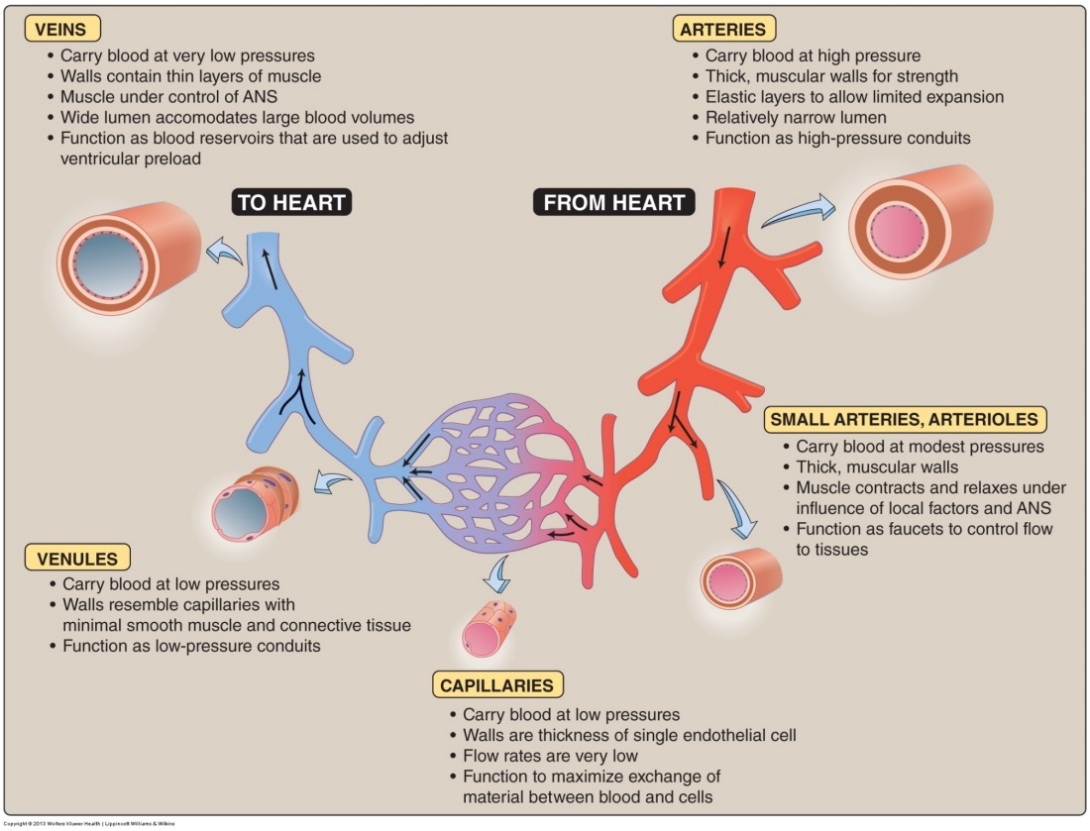

Figure 3 Structure and function of the systemic blood vessels (from Preston & Wilson, Physiology. International Edition ISBN 13-978-1-4511-7567-7)

Fluid exchange between tissue and blood

The exchange of fluid and small substances such as oxygen and carbon dioxide, occurs in the microcirculation. The movement of the gases is covered in the Respiratory Chapter. The movement of fluid across the capillary wall is governed by a set of pressures collectively called Starling forces; hydrostatic pressures in the capillary and in the interstitial fluid, and oncotic pressure (a special type of osmotic pressure exerted by proteins) in the capillary and in the interstitial fluid.

Fluid filtration

Factors which favouring water movement out of the capillary are the hydrostatic pressure in capillary (the blood pressure), which attempts to force fluid out, and the oncotic pressure in the interstitial fluid (this force is negligible as there are very few plasma proteins which escape out of the circulation and into the surrounding interstitial fluid). Osmotic pressure is a force which attracts water (think of it as one which 'sucks' water towards it).

Fluid reabsorption

Factors favouring water movement into capillary are the osmotic pressure of proteins in blood and the hydrostatic pressure of interstitial fluid (again, this force is negligible as the interstitial fluid is more gel-like than fluid-like).

The magnitude of the forces and net fluid movement

As the blood flows through the capillary its hydrostatic pressure falls as this pressure is used up for energy to drive the blood through the circulation. However, it never falls below the oncotic pressure in the capillary (the opposing force). Thus, the balance of forces favours a net movement of fluid out of the capillary along its full length, but diminishes towards the post-capillary venule (see Figure 6). Approximately 8 litres of fluid is filtered across the systemic capillaries per day, and under normal conditions 50% of this is reabsorbed into lymphatic vessels.

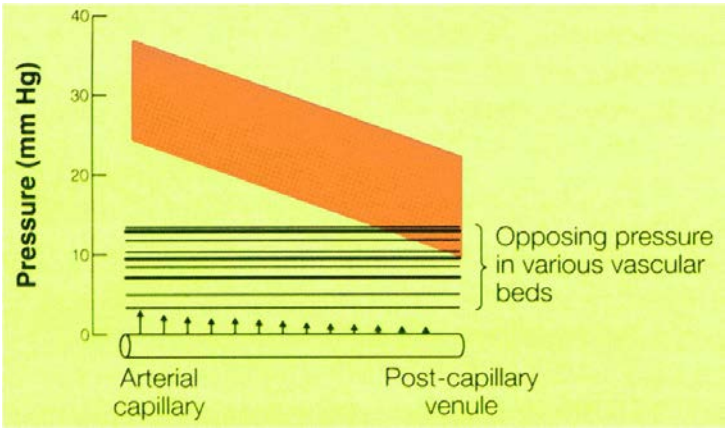

Figure 6 The balance of Starling forces governing movement of fluid out of the capillaries (orange bar denotes hydrostatic pressure in the capillary, the opposing pressure are the oncotic pressures).

Oedema formation

Tissue oedema (swelling due to fluid accumulation) results from a change in Starling forces and a consequent change in fluid exchange across the capillary. The reasons for this are several.

Changes to oncotic pressure

A decrease in plasma proteins (due to either a decreased production as a consequence of liver disease, or increased loss from the circulation due to filtration in the kidney and proteinuria), will decrease capillary oncotic pressure; the force opposing filtration. Thus, filtration of fluid across the capillary wall will increase. Likewise, systemic inflammation can cause the capillaries becoming 'leaky' and allowing proteins to escape from the plasma and into the interstitium. This will increase oncotic pressure in the interstitial fluid, and decrease oncotic pressure in the capillary; drawing water out of the capillary.

Changes to hydrostatic pressure

Heart failure is a condition where the heart muscle is so weak it cannot pump strongly enough to empty sufficiently with each beat (see section; Congestive heart failure). As a consequence, blood backs up into the venous system (in right sided heart failure). This increases hydrostatic pressure within the veins and also as far back as the capillaries. The increased hydrostatic pressure increases fluid filtration across the capillary wall and oedema can occur, particularly in dependent areas such as the ankles in an upright individual. This can

also occur in the lungs (when the left side of the heart fails) resulting in pulmonary oedema and shortness of breath.

The relationship between pressure, flow and resistance

The relationship between pressure, flow and resistance can be described by a modified version of Ohm's law. Ohm's law states that an electrical difference (voltage) between 2 points is generated when ions flow (current) against a resistance. V (voltage) = I (current) x R (resistance). The heart makes blood flow against a resistance which generates a pressure. The haemodynamic version of Ohm's law is thus: P (pressure) = F (flow) x R (resistance). This pressure drives blood through the vascular beds. Thus, we can rearrange the equation to regulate blood flow to individual organs; F = P/R. Therefore if either blood pressure or vascular resistance changes, blood flow to the tissue beds will change. Globally, the haemodynamic version of Ohm's law is;

Systemic blood pressure = cardiac output x total peripheral resistance (**BP = CO x TPR**). The regulation of systemic blood pressure will be covered later in section; Regulation of blood pressure; the baroreceptor reflex.

Cardiac output = heart rate x stroke volume (**CO = HR x SV**). The regulation of cardiac output will be covered later in section; Regulation of cardiac output.

The origin of the heartbeat

The heart is made up of individual cardiac muscle cells called myocytes. For the heart to function efficiently as a pump, these individual cells must beat in a coordinated fashion. The coordination of the heart beat originates with the coordinated spread of electrical activity across the myocytes. This electrical activity leads to the mechanical beat.

Electrical activity

It is important to have an understanding of the electrical activity of the cardiac myocytes, not only to understand the ECG (electrocardiogram), but also to understand how and where drugs act that treat conditions such as rhythm disturbances (e.g., calcium channel blockers, such as verapamil, block or reduce the action of the calcium channels responsible for Phase 0 of the pacemaker action potential – see below, to reduce heart rate in patients with angina and atrial fibrillation).

A membrane potential is the electrical difference (voltage) across the cell membrane due to the difference in the distribution of anions and cations. By convention, the extracellular fluid is considered to be at zero volts and so all electrical potentials are

relative to this. There is a potential (electrical difference) between the inside and the outside of the cell such that inside is negative with respect to the outside, at rest (i.e. when no action potential is being propagated). This is the **resting membrane potential**. If ions are allowed to flow across the membrane, by opening and closing specific ion channels, then this will alter the electrical potential of the membrane (the membrane potential) over time and trigger an **action potential** (see Figure 4). The action potential in a cardiac myocyte, triggers a series of intracellular events, ultimately resulting in contraction of the cardiac muscle fibre (see section X).

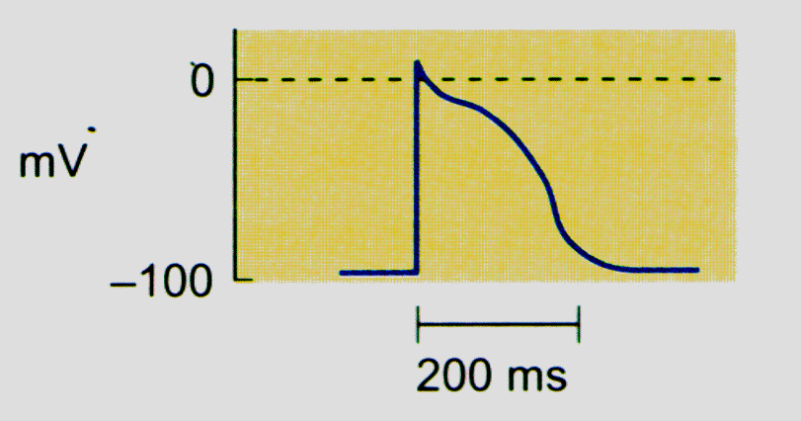

Figure 4 An action potential (from Pocock & Richards, Physiology. 1999)

The resting membrane potential

Ions (charged particles, such as sodium, calcium and potassium) are relatively impermeable at the cell membrane. They can only cross the membrane when their specific channel is open. Due to the concentration difference of ions (set up by pumps on the membrane) inside and outside the cell (between the intracellular fluid and extracelluar fluid) the opening of ion channels leads to movement (diffusion) of ions down the relative concentration gradients. As these ions are charged movement can also occur due to their electrical potential (from a negative environment to a positive environment and *vice versa*; opposite charges attract, like charges repel). When the cell is at rest (no action potential being propagated) some ion channels are open. The resting membrane potential reflects the movement of ions across the cell membrane at rest. Potassium is more abundant inside the cell than outside, thus potassium slowly diffuses out the cell through the potassium-specific ion channel in the cell membrane. As potassium is a positively charged ion, it leaves behind a net negative charge across the membrane. However, the outward movement of potassium is self-limiting as the charge then opposes the movement of potassium ions out of the cell. Net movement stops when the concentration (chemical) gradient exactly opposes the electrical gradient. This is termed the electrochemical equilibrium. The membrane potential at electrochemical equilibrium is the termed the equilibrium potential (E). The equilibrium potential for potassium (denoted E_K) is -90 mV. This is value the resting membrane potential would be if potassium was the only ion diffusing across the cell at rest. However, there is also some small movement of other ions across the cell wall at rest, e.g. sodium (E_{Na} = +61 mV) and calcium (E_{Ca} = +120 mV) and as you can see by their equilibrium potentials they would have the resting cell membrane positive (with respect to the outside of the cell) at rest. Thus, the overall resting

membrane potential (V_m) is calculated from the relative permeability of all the ions that contribute to the membrane potential. A pacemaker cell has a resting membrane potential of -70 mV and a ventricular myocyte -90 mV.

The action potential

An action potential is an ordered change in membrane potential over time (see Figure 4). This occurs by controlled opening and closing of specific ion channels. The purpose of the action potential is to signal to the cell that it must initiate a contraction. When referring to action potentials the following terminology is used (see Figure 5); **depolarisation** refers to the membrane potential becoming less negative (e.g., the membrane potential starts at -90 mV and gets less negative as it moves towards zero), **overshoot** refers to the membrane potential moving above zero (becoming positive), **repolarisation** refers to the membrane potential becoming more negative again (at the end of an action potential) and **hyperpolarisation** refers to the membrane potential becoming more negative (below resting).

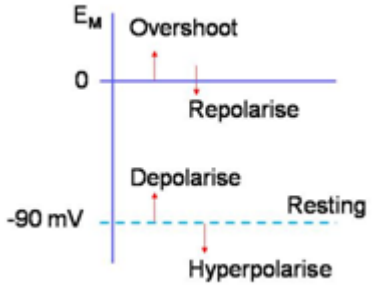

Figure 5 Membrane potential terminology

Pacemakers

The heart has auto-rhythmic properties and pacemaker regions. The electrical activity originates in one of these pacemakers regions; a cluster of myocytes called the **sino-atrial (SA) node**. The SA node found in the right atrium near the superior vena cava (the main vein returning blood from the upper body) and can spontaneously generate action potentials, due to their unstable membrane potential. The SA node cells fire action potentials at a rate of 100 per minute. This rate is altered by the activity in the autonomic nervous system. Activity in the sympathetic nerve increases heart rate and activity in the parasympathetic nerve (cardiac vagus nerve) decreases heart rate. Thus, the resulting normal resting heart rate is around 70 beats per minute. If the SA node fails to fire an action potential the heart does not simply stop, other pacemakers in the heart can take over control of the ~~heart beat~~heartbeat. The **atrioventricular (AV) node** is the next pacemaker in the hierarchy. The AV node is situated, as its name suggests, at the junction of the atria and ventricle in the right side of the heart. The AV node fires at around 50 beats per minute. If the AV node fails a third set of pacemakers can take over the heart beat; these are the myocytes in the **Bundle of His and Purkinje fibres** located in the ventricles. These pacemakers generate action potentials at a rate of around 30 per minute. Both the AV node and the Bundle of His/Purkinje fibre pacemakers are overridden by activity in the SA node under normal conditions. Instead, these regions act as conduction fibres.

Pacemaker action potential

Membrane potential changes in a pacemaker cell occur in phases (see Figure 6). Each phase can be targeted with different drugs for the treatment of conditions such as rhythm disturbances.

Phase 4: the unstable resting membrane potential

This is also termed the prepotential. This unstable (compared to the stable resting potential in a force-producing myocyte) resting membrane potential is the most distinguishing feature of a pacemaker action potential and is the key to automaticity. The action potential in a pacemaker myocyte is generated spontaneously due to the presence of the HCN channel (hyperpolarisation-activated, cyclic nucleotide-dependent nonspecific channel). HCN is a nonspecific cation channel activated by hyperpolarisation of the membrane (which occurs at the end of Phase 3; see Figure 6). The HCN channel has unusual properties in that it allows the simultaneous efflux of potassium and influx of sodium (normally, ions have their own ion-specific channels). The current it generates is thus termed the 'funny current'. The dominant ion flux is sodium and this causes the membrane of the pacemaker cell to slowly depolarise (as the positive sodium ions enter the cell the membrane potential becomes less negative) to the threshold potential for firing an action potential (Phase 0). This phase (the prepotential) is termed Phase 4 in the pacemaker action potential. This slow depolarisation is also influenced by calcium influx and potassium efflux, which is regulated by the autonomic nervous system to change the heart rate.

Phase 0: the action potential upstroke

This phase characterises the upstroke of the slow pacemaker action potential (compared to the fast upstroke in a force-producing myocyte due to sodium influx). It is mediated by calcium influx through L-type calcium channels. The opening of these channels is triggered at the 'threshold potential', about -55 mV during Phase 4. During this phase (0) there is an increase in calcium permeability across the membrane, and the membrane depolarises and overshoots.

Phase 3: Repolarisation

This is the latter part of the action potential, as the membrane is becoming more negative and returning back to its resting potential. It is mediated by inactivation of calcium channels (calcium can no longer enter the cell) and activation of potassium channels (potassium can leave the cell), thus the membrane repolarises. In fact the membrane potential hyperpolarises (becomes more negative than the resting potential) and this triggers the opening of the HCN channels to once again trigger Phase 4.

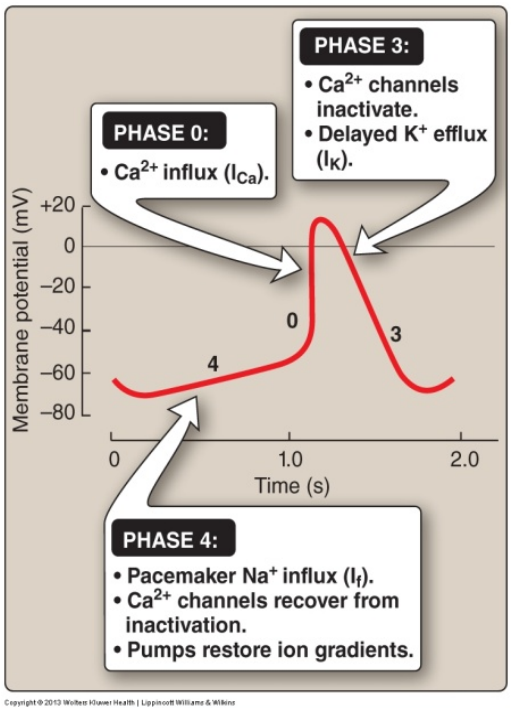

Figure 6 The pacemaker action potential

Effects of the autonomic nervous system on pacemaker firing (changing heart rate)
The SA node (and AV node) is innervated by the autonomic nervous system. The sympathetic nerve releases noradrenaline onto the SA node cell membrane which binds to beta1 adrenoceptors. This increases opening of HCN channels, leading to increased sodium influx via the funny current. This also causes the opening of ligand-gated calcium channels and thus increased calcium influx. The effect of both of these is to increase in slope of prepotential and hence heart rate, leading to an increase in heart rate (a heart rate above 100 beats per minute is termed a tachycardia).

Acitivity in the vagus nerve causes the release of acetylcholine onto muscarinic cholinergic receptors. This decreases the opening of HCN channels, thus decreasing sodium influx. It also slows the opening of calcium channels to decrease~~d~~ calcium influx, and opens an additional set of potassium channels (ligand-gated) to increase potassium efflux. The net result is to hyperpolarise the membrane and reduce slope of prepotential giving a fall in heart rate (a heart rate below 60 beats per minute is termed a bradycardia).

The action potential spreads from cell to cell via gap junctions. Gap junctions are low resistance electrical connections between each cardiac muscle cell (myocyte) and they allow the action potential to spread from cell to cell in a co-ordinated manner from pacemaker cells, to myocytes specialised for conduction, down the conduction pathway (see section on conducting system) and eventually to force-producing myocytes. This allows the contracting heart to act as if it is one big muscle (a functional syncytium).

Myocardial action potential (ventricular myocyte)

The myocardial action potential is initiated by electrical activity from nearby pacemaker action potentials. The wave of depolarisation spreads from pacemaker cells to adjacent force-producing myocytes in both the atria and the ventricles. Compared to the pacemaker action potential, the myocyte action potential has a stable resting potential (see Figure 7), which is more negative (-90 mV) than the pacemaker resting potential. It has a sharp upstroke (compared to the slow upstroke of the pacemaker potential) followed by a partial repolarisation then a long 'shoulder'. There is a long duration (200-300ms) before eventual complete repolarisation. The phases of the action potential are due to the opening and closing of different ion channels. *These phases are important to learn as drugs for cardiac dysrhythmias target different phase.*

Phase 0: Sharp upstroke

The sharp upstroke of the force-producing action potential is initiated at the threshold potential for firing an action potential; ~-65 mV. This charge is spread from nearby depolarising cells. At this membrane potential rapid activation of voltage-gated fast sodium channels occurs, leading to a rapid influx of positively charged sodium ions, thus depolarising the membrane. This phase in the pacemaker cell is initiated by the slower calcium channels, hence the upstroke in these cells is not as sharp as in the force-producing fibre.

Phase 1: Small repolarisation

The action potential begins to repolarise as voltage-gated fast potassium channels open and potassium leaves the cell. The voltage-gated sodium channels are already closed at this point.

Phase 2: Long shoulder

The membrane does not complete depolarisation, as L-type calcium channels (voltage gated) then open and calcium enters the cell, maintaining the depolarisation.

Phase 3: Repolarisation

Repolarisation finally occurs when the calcium channels close and there is a simultaneous opening of slow potassium channels. Potassium can once again leave the cell, bringing the membrane potential back down to its resting voltage.

Phase 4: Return to resting membrane potential

The membrane bound ion pumps (e.g., the sodium-potassium ATPase pump) restore the ion gradients. Sodium and calcium channels re-activate ready for the next action potential.

Refractory period

Unlike skeletal muscle, ventricular muscle cannot undergo a tetanic contraction (a smooth sustained contraction by a fusion of twitches from single action potentials). This would be lethal in the heart as no ventricular filling would occur and the heart would fail as a pump. The reason the heart cannot tetanise is due to its long refractory period; the peak of the mechanical contraction is over before the next

action potential can be initiated. Due to the long shoulder of the myocyte action potential (Phase 2) the absolute refractory period (when another action potential cannot be generated regardless of the size of the stimulus) lasts almost as long as the mechanical contraction. The absolute refractory period lasts between Phase 0 and half way through Phase 3 (the area in the blue box in Figure 7) and is due to inactivation of the fast sodium channels responsible for Phase 0. These sodium channels have 2 gates (both voltage-operated); M and H. Both need to be open for sodium ions to flow. The M gate begins to open at a membrane potential of -65 mV (activation gate) and the H gate also begins to close at this voltage. However, the M gate opens faster (0.1 ms) than H gate closes (1 ms) and so sodium ions can flow into the cell to initiate the upstroke of the action potential. The H gate is closed by the peak of the upstroke and remains closed until half way through phase 3; this is the absolute refractory period. Another action potential cannot generate during this time, until the M and H gate reactivate (M gate closes and H gate reopens) half way through Phase 3 (initiated by the voltage at this point). The relative refractory period occurs between half way through Phase 3 and Phase 4 (resting membrane potential). This is the period of time when individual myocytes are resting sodium channels (occurring at slightly different rates between myocytes), and thus, another action potential could be generated if the stimulus was strong enough. This may be the basis of rhythm disturbances. By the time the action potential is over (Phase 4), all sodium channels have reset and another action potential can be generated.

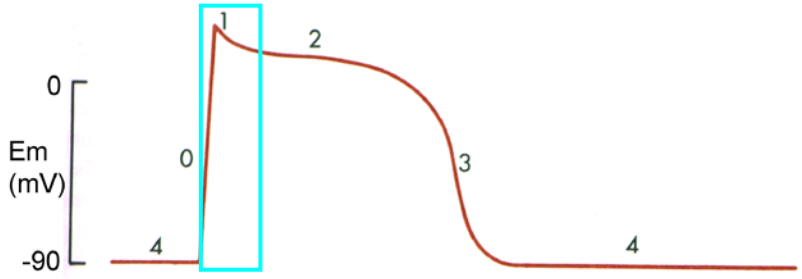

Figure 7 An action potential in a force-producing cardiac myocyte. The area in the blue box is the absolute refractory period.

The electrocardiogram (ECG)

The electrocardiogram (abbreviated to ECG or EKG) provides a functional view of the electrical activity of the heart. This can be a useful adjunct in assessing a patient's condition and must be taken in the context of other clinical findings and the patient's history: it is a tool to aid diagnosis and management, not an end in itself. It is important to stress that it is a record of the net **electrical** activity (wave of depolarisation) spreading across the heart. To obtain information about the **mechanical** activity, other investigations are needed which could include listening to the heart sounds, palpating arterial pulses and recording arterial blood pressure, or even imaging the heart and its resulting blood flow using ultrasound. In extreme cases it is possible to record an ECG but for there to be little or no cardiac output (e.g. during severe cardiac tamponade).

Below is an explanation of each of the parts of the ECG recorded on a Lead II view (as if you are 'viewing' the heart, electrically, from the left hip). There are 12 electrical 'views' of the heart in total; 6 limb leads (I, II, III, aVR, aVL, and aVF) and 6 chest leads (V1-6) but an explanation of these are beyond the scope of this chapter.

Building an ECG

First of all you need to know the 'rules' of the ECG amplifier (see below).You also need to use the figures to follow the text.

Rules of the ECG amplifier:

- If the net wave of depolarisation is travelling towards your viewpoint there is an upward deflection on the ECG.
- If the net wave of depolarisation is travelling away your viewpoint there is a downward deflection on the ECG.
- If the net wave of repolarisation is travelling towards your viewpoint there is a downward deflection on the ECG.
- If the net wave of repolarisation is travelling away from your viewpoint there is an upward deflection on the ECG.
- If there is no net movement of electrical activity the ECG deflection goes back to iso-electric (base) line.

The amount of tissue involved also dictates the size of the deflection.

- If there is only a small amount of tissue, there is a small deflection on the ECG.
- If there is a large amount of tissue involved there is a large deflection on ECG.
- Time is on the x-axis, therefore the width of the waves indicate fast and slow conduction.

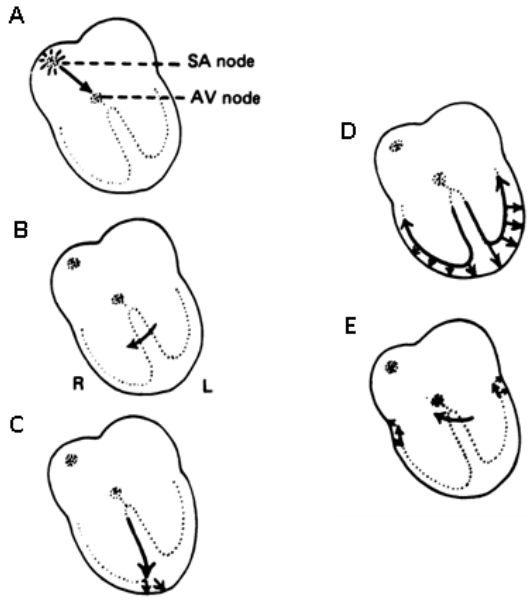

Figure 8 Spread of the net wave of electrical activity across the conduction system of the heart. (From Ganong, Physiology. 1995)

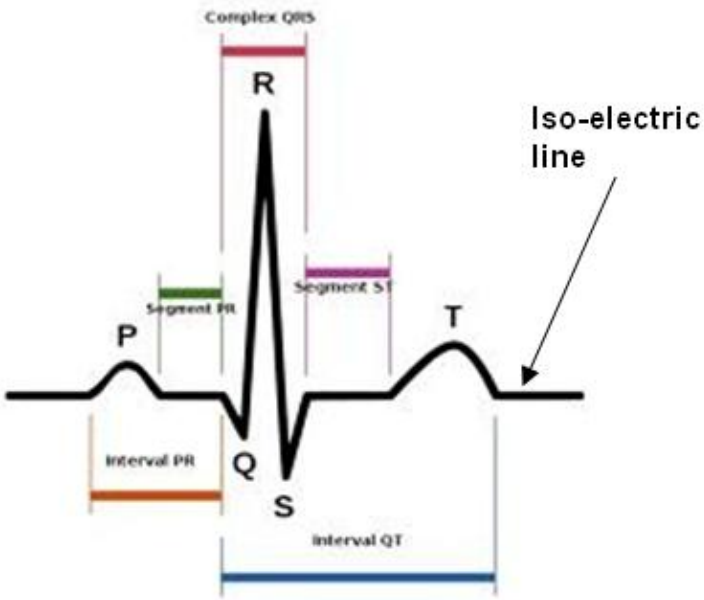

Figure 8 An idealised ECG recorded from Lead II

Conducting system

The conducting system is made up of cardiac muscle fibres specialised for fast, coordinated conduction of the electrical activity (action potentials) that will lead to the mechanical activity of the heartbeat. The full conducting system will be explained in conjunction with its effects on the ECG.

P Wave

The electrical activity originates in the SA node and spreads from cell to cell via gap junctions. The net wave of electrical activity spreads radially across both atria (see Figure 8a). As the atria are only small amounts of tissue, and the net wave of depolarisation is travelling towards the view point in Lead II, hence there is a small upward deflection on the ECG; this is the P wave. When all the atrial myocytes are depolarised, there is no net movement of electrical activity and the deflection on the ECG moves back to the iso-electric line.

The atria and ventricles are separated from each other by a fibrous ring of tissue, which cannot conduct electrical activity except at the atrioventricular (AV) node.

Iso-electric line and PR segment.

When the action potential reaches the AV node conduction slows down. This is to allow adequate ventricular filling and protect the ventricles from high atrial rates in cases such as atrial fibrillation. Once the action potential has navigated slowly through the AV node it travels down the Bundle of His; a thin strip of conducting myocytes that connects the AV node to the interventricular septum (separating the left and right ventricles). This slow conduction is interpreted as no net movement of electrical activity and the ECG moves along the iso-electric line. There is no movement on the ECG until the Q wave (mainly due to the delay at the AV node) and this period of time is called the PR segment.

Q wave
The net wave of depolarisation then travels down the bundle branches (located in the subendocardial surface of the interventricular septum; see Figure 8B). The bundle branches are very thin strips of cardiac muscle cells, thus the amount of tissue involved is relatively small. Due to the anatomy of the bundle branches the wave of depolarisation travels down the left bundle branch slightly before the right bundle branch. Thus, the net wave of depolarisation, whilst travelling down the bundle branches, also jumps across from the left bundle to the right bundle as it travels down the septum. From a Lead II viewpoint the net wave of depolarisation is travelling away and only involves a small amount of tissue, thus this gives a small downward deflection on the ECG: the Q wave.

R wave
The wave of depolarisation (electrical activity) then spreads through the full thickness of the ventricles via the Purkinje fibres (branches of the left and right bundles; see Figure 8C; imagine the arrows are coming out of the page), spreading from the endocardial (inner) surface to the epicardial (outer) surface of the heart, towards the viewpoint of a Lead II. The ventricles have very thick muscular walls (large amount of tissue) and conduction through the Purkinje fibres is extremely vast, thus this results in a sharp and tall upward deflection on the ECG: the upstroke of the R wave.

The net wave of depolarisation then travels up the ventricles (Figure 8D), away from the Lead II viewpoint, there is lots of tissue involved (thick-walled ventricles), fast conduction (up the Purkinje fibres); thus this results in a sharp downward deflection on the ECG back to the iso-electric line; the downward stroke of the R wave.

S wave
The net wave of depolarisation finally reaches the AV ring (Figure 8E). Here there is a small amount of tissue around the ring involved, which is travelling away from the Lead II viewpoint; thus this results in a small downward deflection on the ECG (below the iso-electric line); the S wave.

All the cells in the ventricles are currently depolarised at this point. Thus, the ECG goes back to the iso-electric line as there is no NET movement of electrical activity at this time (this is the S-T segment and corresponds to the long shoulder, Phase 1 on the force-producing action potential). Nothing else happens electrically until the cardiac myocytes in the ventricles repolarise.

T wave
Repolarisation of the cardiac myocytes occurs from the epicardial surface to the endocardial surface (i.e., away from the viewpoint of a Lead II recording). This is because the cells on the endocardial surface have a longer duration of action potential (~300 ms) than the cells of the epicardial surface (~200 ms), thus the outer (epicardial) cells depolarise last but repolarise first. In addition, the cells don't repolarise back up the Purkinje fibre (fast) conduction system. Thus, the net wave of repolarisation of the ventricles is heading away from the Lead II viewpoint and thus

this leads to an upward deflection on the ECG that isn't as sharp as the depolarisation of the ventricles (remember, time is on the x-axis).

Once all the cells have repolarised, and before the next wave of action potentials starts in the SA node again, the line on the ECG goes back to the iso-electric line.

U wave
On rare occasions the T wave may be followed by a U wave. This is thought to be due to papillary muscle depolarisation and is rarely physiologically important.

ECG summary

- The P wave is due to atrial depolarisation
- The QRS complex is due to ventricular depolarisation
- The T wave is due to ventricular repolarisation
- Note the repolarisation of the atria is not evident on the ECG as this the amount of tissue involved is too small to be picked up by the amplifier (and would be masked by the ventricular depolarisation anyway).

From electrical to mechanical activity

Microanatomy of the cardiac myocytes; contractile elements

Cardiac myocytes contain contractile elements consisting of actin (thin filaments) and myosin (thick filaments) that arranged in such a way that the cell appears 'stripy' under light microscopy (thus the cell is said to be striated). The thick and thin filaments are arranged such that they appear to 'slide' over each other during contraction. One whole contractile unit (and there are many in each cell) is called a sacromere (see Figure 9).

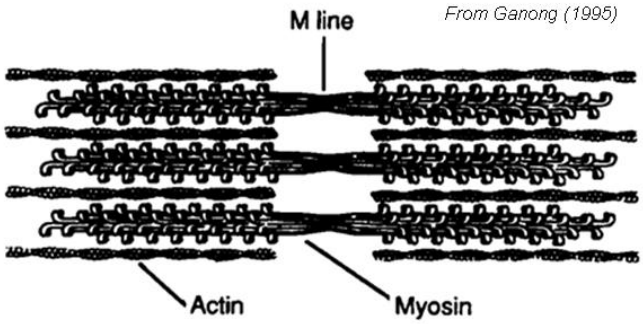

Figure 9 A schematic diagram of a sarcomere; a single contractile unit within a cardiac myocyte.

Contraction is described as cross-bridge cycling and involves the actin strand binding to myosin and actin being 'pulled' into the centre of the sarcomere for shortening of the muscle fibre (contraction). The binding site for actin on myosin is hidden in the non-contractile state, due to the configuration of the actin molecule.

Actin is a protein with a 'rope-like' structure (helical formation). Two strands wrap around each other and a groove is formed along the length of the helix. Another protein molecule, tropomyosin, sits in this groove. Along the tropomyosin molecule are protein complexes containing 3 molecules with different functions; troponin-C (which binds Calcium when it released into the cytosol), troponin-T (which tethers troponin to tropomyosin) and troponin-I (which inhibits the myosin binding site) (see Figure 10).

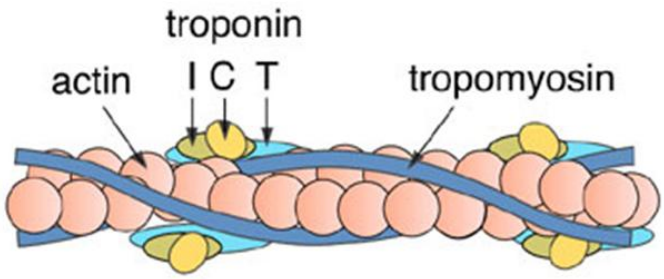

Figure 10 The helical structure of actin (thin contractile filament), with tropomyosin and its protein complex (troponin I, C and T). (From Preston Wilson)

The myosin binding sites remains 'hidden' by troponin I until the cell is ready for contraction. Calcium enters the cell during Phase 2 of myocardial action potential. The amount of calcium entering the cell from the membrane bound calcium channels is insufficient to induce a contraction, but triggers the release of intracellular calcium stores from the sarcoplasmic reticulum (S.R.). This is called calcium-induced calcium release. Calcium then binds to a protein (Troponin C) on the thin filament of the contractile elements within the cell (actin), which leads to a conformational change in the tropomyosin molecule such that troponin I rotates and exposes the binding site for myosin on the actin molecule (see Figures 9 & 10). Cross bridge cycling (contraction) can now occur.

Cross-bridge cycling (contraction)

There are four steps to cross-bridge cycling:

Step 1

The myosin head has ADP (adenosine diphoshate), and inorganic phosphate (P_i) attached to it which energises the molecule. In its energised state myosin has high affinity for actin and binds easily when the binding site is exposed (see microanatomy of the cardiac myocytes; contractile elements). This bound configuration is like a cocked trigger ready to spring (see Figure 11).

Step 2

ADP and Pi are released and this triggers the power stroke; the myosin head pulls the actin into the middle of the sarcomere (only half a sarcomere is shown in Figure 11) and the whole sarcomere shortens.

Step 3
ATP (adenosine triphoshate) binds to the myosin head and reduces its affinity for actin. The myosin head releases from actin.

Step 4
ATP is hydrolysed (split to ADP and Pi) and the myosin head is re-energised, having a high affinity for actin, ready for the next cross-bridge cycle.

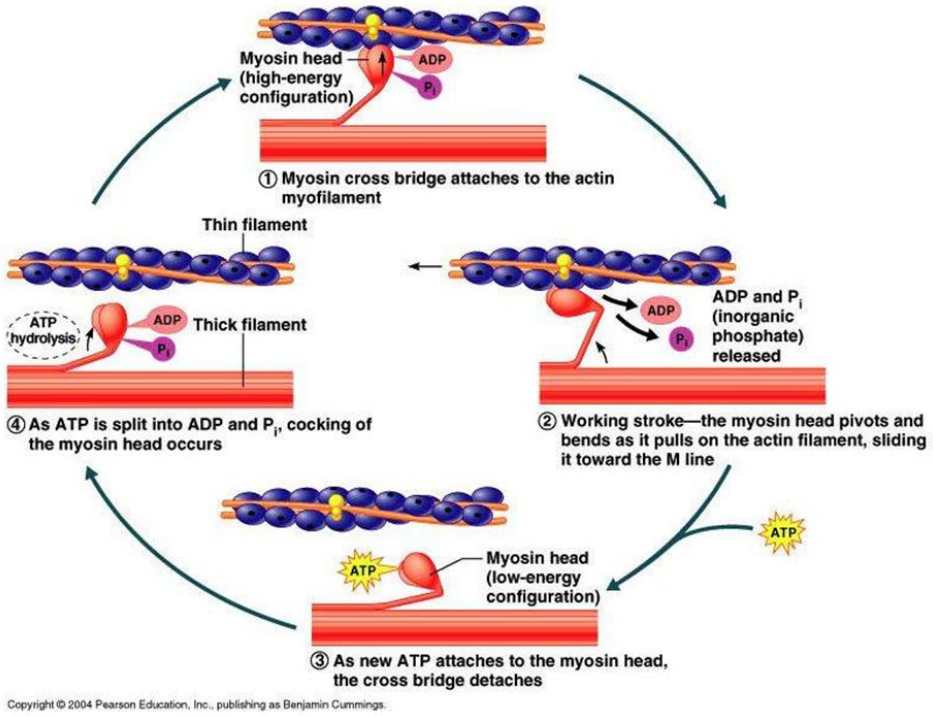

Figure 11 Cross-bridge cycling within a cardiac myocyte. (from Google images!)

Increasing the force of contraction

The force of contraction can be altered by activity in the sympathetic nerves innervating the ventricles. Catecholamines are released from the nerve terminal and bind to beta1-adrenoreceptors on the myocyte cell membrane. This leads to increased calcium influx into the cell via ligand-gated calcium channels, and increased calcium-induced calcium release from the SR. Cross-bridge cycling is dose-dependant on calcium; therefore increased calcium availability leads to increased contraction. The force of contraction can be increased pharmacologically with drugs such as cardiac glycosides (e.g., digoxin and digitoxin) by inhibiting the sodium-potassium ATPase pump that keeps sodium levels in the cell low. This will decrease the sodium gradient that normally drives sodium entry into the cell in exchange for calcium extrusion from the cell. This increases calcium availability in the cell for cross-bridge cycling.

The direction of blood flow through the heart and heart sounds

The passage of blood through the chambers of the heart occurs passively down a pressure gradient, from an area of high pressure to an area with lower pressure.

There are strategically placed ~~one~~ valves between the atria and ventricles (the atrioventricular (AV) valves), and between the ventricles and the main arteries leaving them (aortic and pulmonary valves).

Late diastole
In late diastole, when the heart is relaxing (all the ventricular myocytes are repolarised, corresponding to the long shoulder on the action potential, the ECG will be between the T and P wave), pressure in the ventricles falls lower than in the atria and the AV valves (mitral on the left and tricuspid on the right) open allowing the ventricles to passively fill with blood.

Atrial systole
Following the P wave on the ECG, the atria the contract (following depolarisation of the atria from the SA node through to the AV node) leading to another 20-30% of blood being forced into the ventricles. The aortic and pulmonary (semilunar) valves are closed at this point as pressure is higher in arteries than in the ventricles.

Ventricular contraction
Following the spread of electrical activity across the ventricles (the QRS complex), the ventricles start to contract. Tension (pressure) in the ventricular muscle is building (but there is no shortening of the muscle fibres yet). When pressure is higher in the ventricles than in the atria the AV valves 'slam shut'. This can be heard on the surface of the body with the aid of a stethoscope as the first heart sound (lub). This occurs just after the R wave on the ECG.

Ventricular ejection phase
Pressure in the walls of the ventricles continues to rise and when it is higher than in the main arteries leaving the heart (and atria) the aortic and pulmonary valves open (but the AV valves remain closed due to their one-way configuration). Blood is ejected from the ventricles under high pressure, into the arteries (aorta and pulmonary artery).

Ventricular relaxation phase
Following repolarisation of the ventricular myocytes (T wave on the ECG) the ventricles start to relax. Pressure falls lower in ventricles than in the arteries and the aortic and pulmonary valves slam shut as blood tries to flow down the pressure gradient back into the ventricles. This can be heard as the second heart sound (dub). Thus, this occurs just after the T wave on the ECG. At this point ventricular pressure is still higher than in the atria so AV valves remain closed. Ventricular pressure continues to fall and eventually falls lower than in the atria, causing the AV valves (mitral and tricuspid) to open once again, allowing passive filling of the ventricles from the atria to occur.

Regulation of cardiac output via stroke volume

Cardiac output is the total amount of blood pumped out of one side of the heart (either side, as both ventricles have the same output over the course of a minute) per minute.

The amount of blood pumped out of the heart per minute exactly matches the metabolic needs of the tissues. Any increase in demand for oxygen can met by either increasing heart rate (covered in section; Pacemaker action potential: Effects of the autonomic nervous system on pacemaker firing), or stroke volume (CO = HR x SV). Cardiac output, via stroke volume, is affected by preload, afterload and contractility. Control of SV via preload and afterload involve mechanisms intrinsic to the heart (requires no input from external nerves or hormones), whereas control of SV via changes in contractility involve mechanisms extrinsic to the heart (via input from external nerves and/or hormones).

Preload

As blood enters the ventricles during diastole it stretches the walls (myocytes), increasing the length of the cardiac myocytes before the beat. This degree of stretch of the myocytes due to the volume of blood in the ventricles before it beats is termed **preload**. An increase in end-diastolic volume (EDV) stretches the myocytes further (increasing preload) in diastole and the cardiac muscle cells respond with a bigger force of contraction (generate higher pressure/tension) in systole. This expels the additional blood that entered the heart (stroke volume is matched to venous return). The mechanism behind this length-force relationship (termed **Starling's law of the heart;** see Figure 12) is the number of available cross bridges. When the ventricle is almost empty (low preload) the actin and myosin filaments overlap (less stretch), reducing the number of cross bridges available. As EDV increases this stretches the myocardium giving optimal overlap between thick and thin filaments and providing the maximum number of cross bridges for cross bridge cycling. A full ventricle within the normal operating range will provide optimum number of cross bridges and maximal force can be generated. In addition, stretching of the myocytes increases sensitivity of the cross bridges to calcium, so a bigger force can be generated with the same amount of calcium. The molecular details of this mechanism are currently unknown. If the ventricle becomes too full the myocardium is stretched to its limit and the thick and thin filaments don't overlap. No tension can develop, stroke volume can go down; this can happen in heart failure.

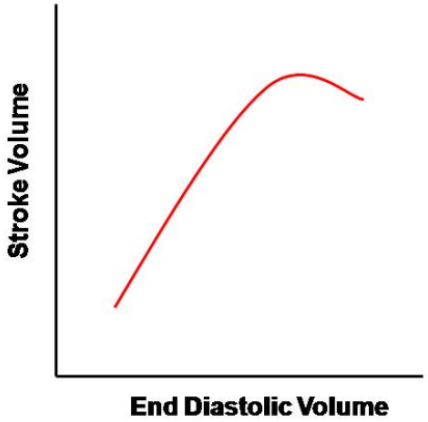

Figure 12 Schematic diagram demonstrating Starling's law of the heart; the relationship between initial cardiac muscle cell length (due to end diastolic volume) and force produced in the ventricles during contraction (manifested as stroke volume).

Clinical application of Starling's law of the heart

Central venous pressure (CVP) is the pressure in the vena cava near the right atrium. CVP is used as a surrogate for end diastolic pressure/volume. Ventricular filling is largely determined by CVP (blood flows down a pressure gradient). An increase in CVP (which can be detected by clinical monitoring) will increase the pressure gradient for blood to enter the right atrium (and eventually the left ventricle). Thus, EDV increases, this stretches the myocytes, and the muscle responds with a greater force of contraction (Starling's law of the heart). Stroke volume increases and thus cardiac output increases.

A premature ventricular contraction (showing as a ventricular ectopic beat on an ECG) will cause an increase in EDV in the next normal conducted beat (as the ectopic beat has no mechanical ejection). This will cause a shift to the right on the steep portion of the Starling curve (see Figure 12) and the heart will respond with a bigger force of contraction (increased stroke volume) to eject the extra blood. The patient will feel this as a 'palpitation'.

Consequently the ventricles will eject a volume of blood during systole equal to that entering during diastole. So SV (stroke volume) is matched to VR (venous return).

Afterload

We have seen how preload affects stroke volume (see above), via Starling's law of the heart. Another force that the heart has to work against to eject blood from the ventricles is called afterload. Afterload is the pressure in the arteries that the ventricles have to work against in order to open the aortic valve and eject blood; in a healthy individual this is arterial blood pressure. An increase in mean arterial blood pressure means that the ventricles have to generate a bigger force (pressure) to get pressure higher in the ventricles than in the aorta and thus open the aortic valve. However the ejection phase is cut short. This is because myocytes have a limited amount of ATP available to develop force during each contraction (to prevent tetany) and they used more to develop a higher force to open the aortic valve (to overcome the higher arterial pressure in the aorta), thus leaving less to sustain contraction (and

myocytes cannot shorten as much at higher pressures). In addition, if aortic pressure is higher, when the pressure in the ventricles starts to fall (onset of diastole), it will fall lower than in the aorta sooner and the aortic valve will close earlier. The ejection phase is cut short and stroke volume falls.

Contractility/ Inotropy

Contractility refers to the ability of the heart to change the force of contraction without an initial change in end diastolic volume (the term is synonymous with inotropy). Contractility is dependent on cytosolic calcium availability (see sub-section, Increasing the force of contraction); more free calcium in the myocytes equals stronger force of contraction. Cytoslic calcium can be changed both pharmacologically and by changes in activity in the sympathetic nerve to ventricles. Agents that increase the force of contraction (cause a positive inotropic effect; ~~in~~ increase in SV for a given EDV) are catecholamines (adrenaline and noradrenaline, also digoxin, although this is rarely used in practice now). Whereas beta-blockers (e.g., propanolol) and calcium channel blockers (e.g., diltiazem) have a negative inotropic effect (a decrease in SV for a given EDV).

In practice all three of these physiological variables (preload, afterload and contractility) act simultaneously to control cardiac output, and hence blood pressure on a beat to beat basis. The ultimate aim is to match oxygen supply with the demand from the tissues.

Regulation of blood pressure; the baroreceptor reflex

What generates blood pressure?

Before discussing its regulation, it is important to gain an understanding of what generates blood pressure. Arterial blood pressure is the pressure needed to drive blood to the tissues for the delivery of oxygen (perfusion pressure). It is recorded as systolic over diastolic pressure; that is pressure in the arteries during systole and pressure in the arteries during diastole. During systole the heart pumps blood into the arteries faster than it can reach the capillaries. Arteries are elastic structures that distend to accommodate the full SV and absorb some of the pressure energy from the blood being pumped through it, and this dampens the pulse. This energy is then used to drive the blood through to the capillaries during diastole when the heart is not pumping (converting an intermittent flow into a continuous flow like a Windkessel fire engine). Thus, stroke volume determines systolic blood pressure.

Diastolic pressure is due to the volume of blood in the arteries during diastole and so is due to arteriolar resistance (a higher vascular resistance will make it harder for blood to leave the arteries and so more stays behind in the artery = higher diastolic BP)

Aging leads to calcification and collagen deposition in arterial walls (arteriosclerosis), they stiffen and cannot expand as much during systole, and thus cannot store as

much blood during systole for later runoff in diastole. Thus, the heart has to generate higher pressures to drive increased flow during systole for adequate diastolic runoff. This is **essential hypertension** and is common in older adults.

Mean blood pressure is the pressure in the arteries averaged over time (area under the curve/time), it's not just the difference between systolic and diastolic (as there is more time spent in diastole); that is the pulse pressure.

The moment-to-moment control of blood pressure

It is the role of the kidneys to regulate long term arterial blood pressure via control of blood volume. However, the most important mechanism for the moment-to-moment control of blood pressure is the arterial baroreceptor reflex. As mentioned in the section; Relationship between pressure, flow and resistance, the haemodynamic version of Ohm's law describes the building blocks of blood pressure; BP = CO x TPR. Cardiac output is regulated by heart rate (covered in sub-section; Effects of the autonomic nervous system on pacemaker firing, changing heart rate) and stroke volume (covered in section; Regulation of cardiac output via stroke volume). What remains to be discussed is resistance to blood flow (total peripheral resistance is the sum of the reciprocal resistance of each vascular bed, as the systemic circulation is arranged in parallel), and the baroreflex as a whole.

Resistance to blood flow

Blood pressure is needed to drive the blood through the blood vessels against a resistance. Resistance is determined by the blood viscosity, vessel length and radius. As vessel length and blood viscosity are not easily and quickly modified, for the purpose of the control of blood pressure, vessel radius is the more important parameter to consider. Thus, according to Poiseuille law resistance is inversely proportional to the vessel radius to the power 4. This means that even small changes in vessel diameter will result in large changes in resistance (and hence BP, as BP = CO x TPR).

Vessel diameter is under the control of the sympathetic nervous system (see section; Structure and function of the blood vessels, arterioles). Increased activity in the sympathetic nervous system leads to increased release of adrenaline or noradrenaline, which acts in the alpha1-adrenoreceptors. This causes constriction of the smooth muscle surrounding the vessel (mainly the arterioles) to reduce the radius and increase the resistance.

The baroreflex

The baroreflex is a negative feedback mechanism which maintains arterial blood pressure constant on a beat to beat basis. The actions affect heart rate, stroke volume, vascular resistance (in the arterioles) and venous capacitance.

Receptors

The receptors which monitor arterial blood pressure are located in the walls of the carotid sinus (a slightly widened area of the internal carotid artery) and in the wall of the aortic arch. They are sometimes called high pressure baroreceptors, not because

they only respond to high blood pressure, indeed they respond to both increases and decreases in blood pressure, but because they are on the high pressure side of the circulation (arteries). They are mechano-receptors which respond to degrees of stretch due to the blood pressure within that vessel. The receptors are tonically active, this allows them to quickly respond to both increases and decreases in blood pressure.

Baroreceptor response to changes in blood pressure
Increased blood pressure causes increased frequency of action potentials to brain via the efferent pathway (the sinus nerve from the carotid sinus baroreceptors, and the vagus nerve from the aortic arch baroreceptors). Decreased pressure causes decreased frequency of action potential via the same route.

Operation of the baroreceptor reflex
The autonomic nervous system responds to baroreceptor stimulation (increased BP) or unloading (decreased BP) to affect several organs to bring BP back to normal. We will now consider the operation of the baroreflex in response to a fall in arterial BP. The decrease in blood pressure is detected by a decrease in frequency of action potentials to the brain. The first part of the autonomic nervous system to respond is the vagus nerve (the afferent vagus nerve to the heart). Activity in the vagus nerve is decreased, thus there is a decrease in the release of the neurotransmitter acetylcholine from the nerve terminal onto muscarinic cholinergic receptors on the cell membrane of the SA node and AV node myocytes. This increases the frequency of firing of action potentials in the pacemaker cells, and thus heart rate speeds up. This is the first step to bringing BP back up to normal (as BP = CO x TPR and CO = HR x SV).

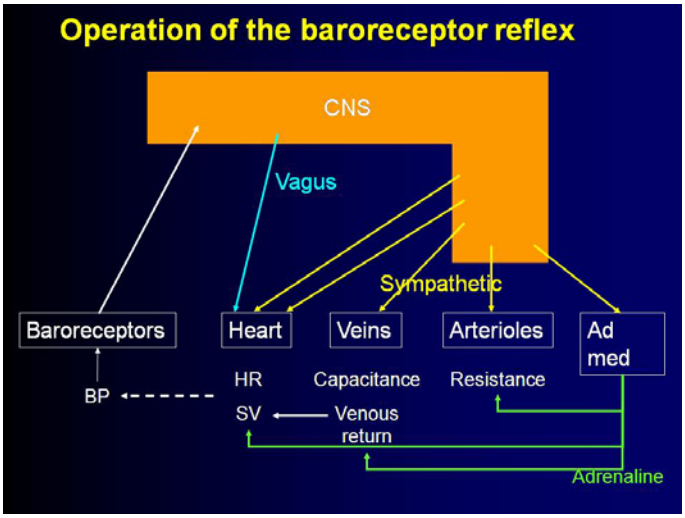

Figure 13 The operation of the baroreceptor reflex. See text for the direction of change of each of the parameters in response to a decrease in blood pressure (an increase in blood pressure has the opposite effects).

A decrease in blood pressure also increases activity in the sympathetic nerves to all areas of the heart. Increased activity in the sympathetic nerves lead to increased noradrenaline (in the main) released from the nerve terminals. Thus, there is more of the neurotransmitter to bind to beta1 adrenoreceptors. The resultant effects are to

increase both heart rate and force of contraction. Noradrenaline released from the nerve terminals innervating the arterioles is also increased. Noradrenaline acts on the alpha1 adrenoreceptors to cause vascular smooth muscle contraction and thus vasoconstriction, vessel radius decreases and vascular resistance increases. In addition to all this, there is more adrenaline released from the adrenal medulla leading to further potentiation of the above sympathetic affects.

The veins are also innervated by the sympathetic nervous system and activity in these nerves is also increased in response to a decrease in BP. Thus more noradrenaline is released from the nerve terminal to act on alpha1 adrenaoreceptors on the venous sm~~a~~ooth muscle. The veins constrict, mobilising some blood from the venous reservoir to give a boost in circulating blood volume, venous return, EDV and (by Starling's alw of the heart) stroke volume; and hence boost blood pressure.

Thus, in response to a decrease in BP, the baroreceptor reflex has increased heart rate, force of contraction (to increase SV), and increased vascular resistance. The boost in venous return from decreasing venous capacitance (how much blood the veins can hold) will increase SV also. Utilising the heamodynamic Ohm's law (BP = CO x TPR and CO = HR x SV) all this will decrease BP back to normal levels.

Hypertension

There are many causes of hypertension. The causes can be split into two main categories; those that are due to increased cardiac output (e.g., high blood volume, stress, and increased catecholamine secretion from a tumour of the adrenal gland; pheochromocytoma) and those that are due to increased systemic vascular resistance (e.g., essential hypertension, stress, atherosclerosis, renal artery disease, thyroid dysfunction, diabetes, pheochromocytoma and Cushing syndrome).

Treatment

It is important to treat hypertension as this condition can lead to myocardial infarction, stroke and kidney disease. There are many ways to pharmacologically target hypertension. The increased resistance can be targeted by treating with vasodilators (such as hydralazine or calcium channel blockers). High blood volume can be treated with diuretics (e.g., frusemide). The increased cardiac output can be targeted with drugs which slow down the heart rate and force of contraction (e.g., beta-adrenergic antagonists, 'beta-blockers'). Beta-blockers (e.g., propanol~~-ol~~) should never be prescribed to patients with diabetes or asthma as they exacerbate those conditions due to the beta receptors they target?~~.~~

Common cardiac pathophysiologies

Angina

Angina is chest pain caused by an imbalance in oxygen supply and demand. Insufficient oxygen is delivered to the myocardium to meet~~s~~ its oxygen needs. Often the cause is a narrowing of the lumen of the coronary blood vessels supplying the

ventricular muscle. This can be caused by plaque formation in the walls of these vessels (atherosclerosis), or coronary artery spasm (pPrinzmetal, or variant angina).

Symptoms
Patients may experience chest pain with tachycardia, hypertension, sweating, nausea and sometimes breathlessness.

Treatment
Treatment of angina is aimed at redressingrestoring the oxygen supply/demand imbalance. GTN (glycerol trinitrate) is a spray that patients can administer themselves when they feel the onset of chest pain. It acts by dilating the veins and arteries to reduce the work (and hence oxygen demand) of the heart by reducing preload and afterload. Other forms of treatment aim to reduce the chances of a subsequent myocardial infarction (e.g., beta-blockers, calcium channel blockers, statins and aspirin).

Myocardial Infarction

Myocardial infarction oOften referred to as 'heart attack', a myocardial infarction is irreversible damage or death of heart muscle cells (necrosis). This occurs when heart muscle is deprived of oxygen for a prolonged length of time (20-30 mins) through insufficient blood flow to the heart muscle itself. Typically a clot breaks off from an atherosclerotic plaque, and this occludes the vessel. The cells which this vessels supply quickly run out of oxygen to make ATP for contraction, and this impairs the contractile function of the heart.

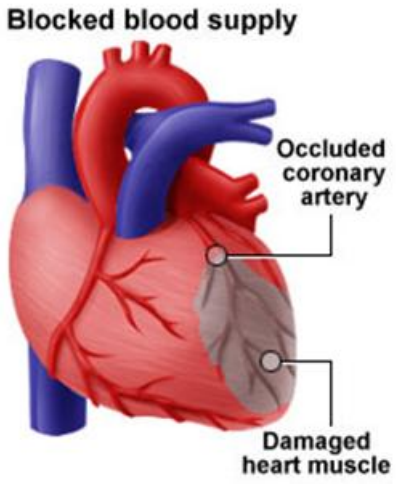

Figure 14 Pathology of a myocardial infarction (stolen from Chaytor's lecture notes)

Symptoms
A patient experiencing an MI can experience any of the following; prolonged severe chest pain chest, pain in the throat, arms, back or epigastrum, breathlessness, anxiety, nausea and vomiting. The patient may also collapse.

Treatment

Immediate treatment, if available, would be administration of oxygen to relieve the hypoxia, Morphine/diamorphine with an antiemetic to relieve pain, anxiety and nausea. Nitrates such as GTN spray reduce the oxygen demand (and thus cardiac work) by venodilation and vasodilation (the patient will often be carrying one). Thrombolytic agents can be administered to dissolve any clots (e.g., Alteplase/Reteplase). Finally anti-platelet therapy would be given to prevent further clot formation (e.g., aspirin, Clopidogrel).

Subsequent treatment is aimed at preventing further events. Thus, patients will be prescribed beta-blockers to improve ~~s~~myocardial perfusion (these drugs slow the heart down giving more time in diastole, which is when the coronary arteries are perfused) and prevents arrhythmias developing. ACE inhibitors, such as captopril, will reduce blood volume if there is risk of heart failure developing. Anticoagulants such as Heparin may prevent reinfarction. Nitrates, antiarrhythmic drugs and statins (lipid lowering drug) are also likely to be prescribed long-term.

Cardiac arrhythmias

The normal heart rhythm originates in the SA node, and is thus called sinus rhythm. However, abnormal rhythms can be triggered from any part of the heart..

Atrial arrhythmias

These tend to cause fast heart rates. Common ones are atrial fibrillation and heart block.

Atrial fibrillation

Atrial fibrillation (AF) is a relatively common arrhythmia, particularly in elderly patients and in patients with heart failure. It is caused by chaotic electrical activity originating in the atria (individual cells depolarising at random). There is no coordinated spread of electrical activity across the atria and thus no discernable P wave on the ECG. Instead they are replaced by continuous irregular fluctuations called F waves. The atria do not contract and thus cardiac output is reduced by 20-30%. The ventricles are protected from a potential high frequency of action potentials arriving at the AV node and leading to ventricular tachycardia. The AV node is protective in this way due to the slow conduction of action potentials through it and the long refractory period of the myocytes. However, conduction of the electrical activity into the ventricles is random and thus the QRS complexes are irregular. Treatment is aimed at slowing down the heart rate with drugs such as beta-blockers. Anticoagulants may also be prescribed as patients are susceptible to strokes due to clots being formed in the atria and released into the circulation.

Atrioventricular block (heart block)

Atrioventricular (AV) block is a delay or interruption to the transmission of electrical activity through the AV node. There are several types:

- First degree heart block: P-R interval is prolonged
- Second degree heart block: there are two types; Mobitz type 1 (or Wenckebach) is characterised by a progressive lengthening of the P-R interval

until transmission fails to conduct one complex, then the system resets and starts again. In Mobitz type II a QRS complex is dropped without prior warning. This type is more dangerous as it can progress to third degree heart block.

- Third degree heart block: there is a complete block between the atria and ventricles electrically. The atria and ventricles each beat at their own pace completely independent of one another (ventricular pacemakers take over the heart beat). The ventricular rate is very slow (~30bpm) and thus cardiac output is low. This is one of the most common reasons for a pacemaker to be fitted.

Ventricular dysrhythmias

Rhythm disturbances can also originate in the ventricles. Ventricular ectopic beats are single random premature depolarisation of a myocyte. The electrical activity spreads across the myocardium in a random manner (not down the usual fast conduction system), thus this results in a wide QRS complex on the ECG. Often these ectopic beats are singular and result in no mechanical output, thus the next beat has a high stroke volume due to the longer filling time. This beat will be experience by the patient, who often describe it as a 'palpitation'. Occasionally these ectopic beats can pace the heart at very high rates this is known as ventricular tachycardia (V-tach).

Ventricular tachycardia

V-tach can be very dangerous as cardiac output drops to very low values at such high rates. The myocardial oxygen supply will also suffer as a consequence and this can progress into ventricular fibrillation (VF).

Ventricular fibrillation

VF is the most dangerous rhythm disturbance as this leads to death of the patient within 3 minutes. There is disorganised electrical activity in the ventricular myocytes, thus no coordinated spread of electrical activity and no mechanical output. Blood pressure quickly falls and the patient loses consciousness within minutes. The heart needs to be immediately electrically stimulated (with an automated electrical device; AED) to force the SA node into firing action potentials and restarting the heart.

Treatment of arrhythmias

Antiarrhythmic drugs are used to treat the abnormal rhythms mentioned. The treatment options depend on the cause of the arrhythmia. There is a range of drugs that affect the cardiac action potential and they are classified depending on their main action by the Vaughn Williams classification. Examples of treatment types are beta-blockers (e.g., propanolo), and sodium (e.g., quinidine) and calcium (e.g., verapamil) channel blockers.

Congestive heart failure

Heart failure is a condition where the heart fails to pump out a volume of blood matching the volume that enters the heart (this can occur following a myocardial

infarction). Thus, EDV increases and this overstretches the heart, reducing its ability to form cross bridges, and reduces contractility. The bigger the left ventricle (and thus the greater the radius and the thinner the wall), the greater the wall tension (left ventricular pressure) needed to eject the same volume of blood per beat than a normal, undilated heart. Thus cardiac work (and hence oxygen demand) increases in a patient with heart failure. With left-sided heart failure the heart fails to pump forward adequately into the system circulation and blood 'backs up' into the pulmonary circulation. This increases hydrostatic pressure (blood pressure) within the pulmonary capillaries and fluid can be filtered out into the surrounding interstitial fluid (or even into the alveoli if the pressure is high enough). This increases the barrier for gas exchange (see Respiratory Chapter) and leads to low oxygen tension in the systemic arterial blood. The most common cause of left sided heart failure is hypertension. The increased pulmonary pressure puts extra work on the right side of the heart and this can eventually lead to right-sided heart failure (the most common cause of right sided heart failure is left sided heart failure). Central venous pressure (CVP) will increase as the right side of the heart fails to pump forward into the lungs and blood 'backs up' into the venous system. The increased pressure in the systemic venous system leads to fluid movement out of the systemic capillaries and tissue oedema in dependent parts of the body (e.g., the ankles). The raised CVP can be used to assess your patient in suspected congestive right-sided heart failure. Heart failure can cause some arrhythmias due to stretching of the ventricular walls and the conduction pathway.

Symptoms

Patients may experience reduced exercise tolerance, hypotension, tiredness and dizziness. Urine flow may be reduced as there is reduced forward flow to the kidneys. Cold peripheries may be felt, breathlessness, oedema and atrial fibrillation.

Treatment

There are 3 major approaches to dealing with heart failure;

1. Diuretics; these drugs reduce circulating blood volume and reduce pulmonary congestion. However, excessive diuresis may cause further hypotension
2. Vasodilators; these reduce preload and afterload to reduce the work of the heart
3. Positive inotropes; to increase muscle contractility and increase stroke volume.