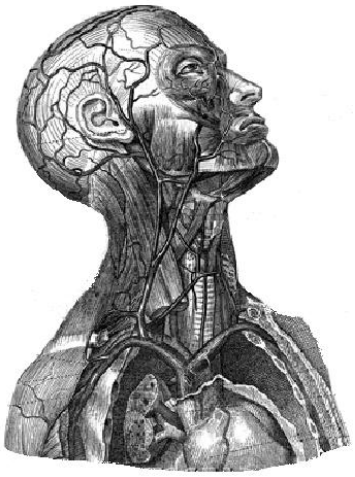

Cardiovascular Physiology

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Aim

The overall aim of this set of four lectures is to introduce you to the heart and circulation and the control of cardiovascular function.

Lecture 1: Overview

In this lecture we will discuss why having a circulatory system is necessary. We will discuss the relationship between diffusional distance and diffusional time. We will review the anatomy of the heart and the vasculature. Introduce the concept of a double circulation and the peculiarities of the right heart function and the pulmonary circulation. Finally, we will discuss the characteristics of the circulation before and after birth.

Lecture 2: Regulation of cardiac function

In this lecture we will focus on the heart, starting with the electrical, audible and mechanical events in the cardiac cycle. I will teach you how to construct cardiac pressure-volume loops and their importance in the assessment of cardiovascular health and disease. We will expand on the intrinsic and extrinsic control of cardiac function. We will review the experiments that gave rise to the Starling Law of the heart and expand on the neural and endocrine control of cardiac function.

Lecture 3: Regulation of vascular function

In this lecture we will talk about haemodynamics and review what makes blood flow and why. We will discuss the concept of vascular resistance and the idea of a sympathetic tone. We will compare and contrast neural, endocrine and local mechanisms regulating the constriction and dilatation of blood vessels, including venomotor tone. We will expand on the discovery of nitric oxide (NO) and its importance in the control of vascular function. I shall introduce you to pressure waveforms and the measurement of arterial blood pressure.

Lecture 4: Brainstem integration of reflex control

The final lecture in this set will focus on the integration of information from baroreceptors and chemoreceptors by the cardiovascular centre in the medulla oblongata. We will review cardiac and vasomotor baroreflex responses. We will expand on the physiology of baroreception and chemoreception and the concepts of receptor set-point, sensitivity and resetting. Finally, we will establish the differences between primary versus secondary chemoreflex responses to hypoxia.

Reading List

This handout is the compilation of information obtained from several textbooks, previous handouts and established and recent research papers. Most general physiology textbooks are appropriate for information on basic cardiovascular physiology. However, a textbook that I particularly like is Levick's '*An Introduction to Cardiovascular Physiology*, published by Butterworth-Heinemann.

Lecture 1. Overview

1.0. What does a heart do and why?

All cells need oxygen and nutrients to survive. Small primitive organisms lack a cardio-vascular system because their needs can be met by direct diffusion from the environment, and even in man diffusion is the fundamental means of transport between blood and tissue. The problem arises with transport across distances too long for diffusion to cope with. Long distances occur as a result of cells clustering together to form more complex organisms. These clusters of cells can begin to form tissues with specialized functions, and particular structural roles that allow an organism to exploit new resources. These resources can occur in new environments presenting 'temporal' challenges to organisms. Examples of these are the need to react to daily environmental fluctuations, such as strong sunlight or strong winds or the need to escape from predators. Rapid reactions require cells with high metabolic rates. These high rates require high fluxes of metabolites (a substance produced or used during metabolism), which is impossible with simple diffusion. As Albert Einstein showed, the time *t* that it takes a particle to move a distance *x* in one specific direction increases with the square of the distance: $t \alpha x^2$. Consequently, transport by diffusion is extremely slow over long distances. Consider Table 1. Over short distances, like the neuromuscular gap junction (0.1 μm) diffusion takes only 5 millionths of a second, whereas across the heart wall (about 1 cm) it is hopelessly and catastrophically slow, taking over half a day!

Table 1. Diffusional Transport

Time taken for an oxygen or glucose molecule to diffuse a specified distance in one direction

Distance	Time	Distance *in vivo*
0.1 μm	0.000005 s	Neuromuscular gap
1.0 μm	0.0005 s	Capillary wall
10 μm	0.05 s	Cell to capillary
1 mm	9.26 min	Skin or artery wall
1 cm	15.5 hours	Ventricle wall

Sadly, nature often proves the validity of Einstein's equation and this is represented in Figure 1. It shows the heart of a patient who suffered a cardiac infarct and sudden death. An infarct is a condition characterised by the formation of a dense wedge-shaped block of dead tissue in the heart muscle following an interruption to its blood supply. Heart tissue dies when deprived of oxygen and the patient had a 'heart attack'. The pale area is muscle that died from ischaemia – lack of oxygenated blood supply to tissue. The irony is that this is despite copious amounts of richly oxygenated blood present in the adjacent cavity - the ventricle. The patient died simply because a distance of a few millimetres reduced diffusional transport to an inadequate rate.

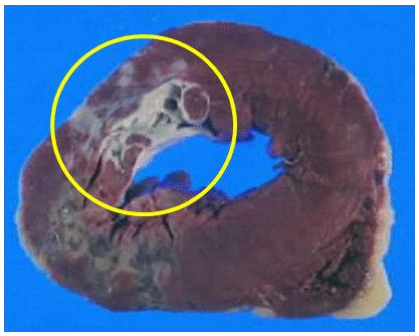

Figure 1. Heart attack. The pale area is the result of a cardiac infarct.

Hence, the primary function of the circulatory system is to overcome the problem of how to move chemicals long distances at reasonably high speed. Most circulatory systems have a pump. The heart convert chemical energy stored within the blood (e.g. glucose) to mechanical (pressure) energy, which then causes bulk flow. Bulk flow takes the chemicals closer to the tissue where diffusional transport takes over.

1.1. Evolution of closed circulatory systems

Vertebrates have independently evolved closed circulatory systems in close association with the respiratory systems. In fish, such as a water breathing teleost like the trout, blood flows from the heart to the gills for gas exchange, then to the rest of the body, and finally back to the heart. This is called a *single circulation* since the blood flows through the heart only once during each complete trip around the body (Figure 2).

Amphibians, reptiles, birds and mammals have evolved a *double circulation*; blood flows from the heart to the lungs for gas exchange, then back to the heart to be re-pressurized before flowing to the rest of the body (Figure 2). The vessels that serve the respiratory organs are called the branchial circuit (for gills) or pulmonary circuit (for lungs). Vessels that

serve the rest of the body are called the systemic circuit.

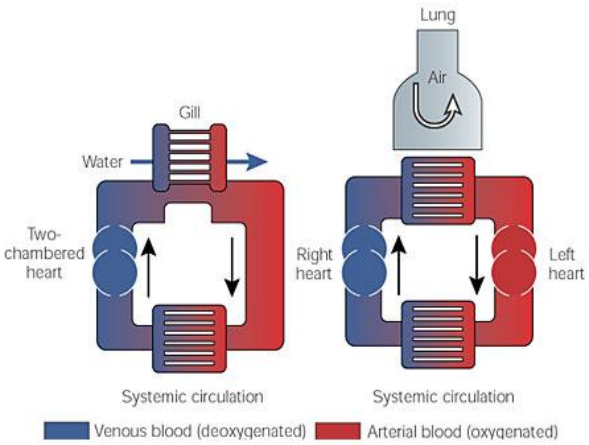

Figure 2. Double circulation

1.2. Detailed arrangement of the mammalian circulation

The blood vessels consist of arteries, arterioles, capillaries, venules, and veins. All blood is carried in these vessels. The arteries carry blood away from the heart and bear the highest blood pressures. The artery that takes blood away from the heart to the systemic circulation is called the *aorta*. The arteries branch into smaller and smaller vessels, eventually becoming very small vessels called arterioles. Capillaries are tiny, extremely thin-walled vessels that act as a bridge between arteries (which carry blood away from the heart) and veins (which carry blood back to the heart; Figure 3). The thin walls of the capillaries allow oxygen and nutrients to pass from the blood into tissues and allow waste products to pass from tissues into the blood. Blood flows from the capillaries into very small venules, then into the veins that lead back to the heart. Blood returns to the right side of the heart via the superior *vena cava* and inferior *vena cava.* The right ventricle pumps blood to the lungs for oxygenation. The vessel that carries blood from the heart to the lungs is called the *pulmonary artery. The* pulmonary *veins* return oxygenated pulmonary blood to the left atrium. The pulmonary artery is an exception to the circulation, as it is the only artery that carries deoxygenated blood.

William Harvey (April 1, 1578 – June 3, 1657) was an English medical doctor, who is credited with being the first to correctly describe, in exact detail, the properties of blood being pumped around the body by the heart (*De Motu Cordis*, 1628 - Concerning the Movement of the Heart). It is also widely believed that the Spanish physician Michael Servetus discovered the direction of the circulation a quarter century before Harvey was born, but that all three copies of his manuscript *Christianismi Restitutio* were destroyed. As a result, the secrets of circulation were lost until Harvey rediscovered them nearly a century later.

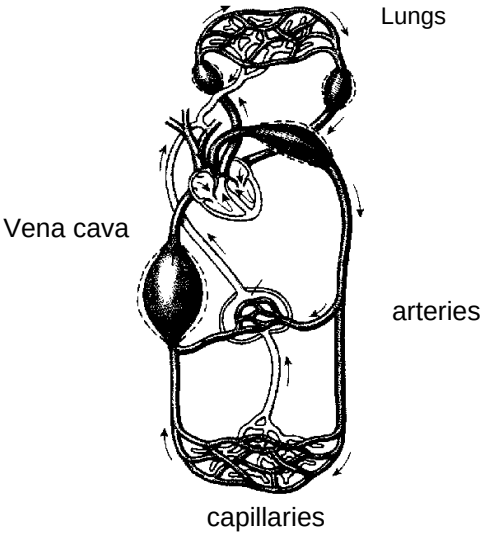

Figure 3. Schematics for the plumbing of the adult mammalian heart and circulation

1.3. Gross structure of the heart

Over an average human lifetime the heart may pump ~200,000,000 litres of blood, the equivalent of around 500 swimming pools. The total work done by the heart over this period is ~240,000,000 Joules (enough energy to raise 16 elephants to the top of Mount Fuji!...apparently).

The heart is located within the pericardial sac, the lower surface of which is attached to the diaphragm so that normal breathing tends to rock the heart.

The heart is constructed around a 'skeleton' of collagen which forms the junction between the atria and ventricles. The *annulus fibrosus* holds the cardiac valves: The atrio-ventricular or AV valves, and the semi-lunar or arterial valves (Figure 4). The AV valves are formed from thin flaps of tissue joined at the base of the connective ring. The flaps connect to collagenous tendons, known as the *chordae tendinae* (Figure 5). Most of the chordae fasten to the edges of the valve flaps. The opposite ends of the chordae are tethered to mound-like extensions of ventricular muscle known as *papillary muscle*. These muscles provide stability for the chordae, but neither

the papillary muscles nor the chordae actively open and close the AV valves. When the ventricle contracts, blood pushes against the bottom side of its AV valve and forces it upwards into a closed position. The chordae tendinae prevent the valve from being pushed back into the atrium, rather like the struts on an umbrella, keeping it from turning inside out. The two AV valves are not identical. The valve that separates the right atrium from the right ventricle is known as the *tricuspid valve* – three cusps. The valve that separates the left atrium from the left ventricle is called the *mitral valve* because it resembles the mitre – headwear of popes and bishops. You can match the correct AV valve to the correct side of the heart by remembering that the Right Side has the Tricuspid (R-S-T). The semi-lunar valves separate the ventricles from the main arteries. The *aortic valve* is between the left ventricle and aorta. The pulmonary valve sits between the right ventricle and pulmonary artery.

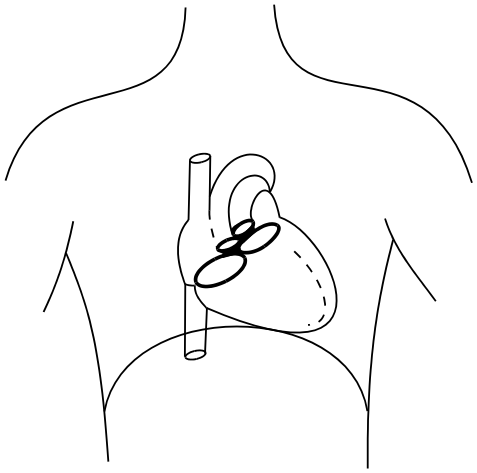

Figure 4. The location of the heart and fibrotendinous ring in man

Both sets of semi-lunar valves have three cup-like leaflets that snap closed when blood attempting to flow back into the ventricles fills them. Because of their shape, the semi-lunar valves do not need connective tendons as the AV valves do.

1.4. Gross structure of blood vessels

All blood vessels, except capillaries, have the same general structure of three layers: The tunica *intima*, the tunica *media* and the tunica *adventitia* (Figure 6). The inner lining of blood vessels is a thin layer of endothelial cells or endothelium, a type of epithelium.

Figure 5. The cardiac valves

The endothelium and its elastic connective tissue together form the *tunica intima*. The media contains a dense population of smooth muscle cells, organised concentrically, with bands or fibres of elastic tissue. The adventitia, which contains a collagenous extracellular matrix containing fibroblasts, blood vessels and nerves, and functions to add rigidity and form to the blood vessel.

The tunica media varies in thickness in different blood vessels according to their function. For instance, large elastic arteries, such as the aorta, have a thick media so it can expand and recoil during ventricular contraction and relaxation, thereby smoothing the pressure changes. Thus, these vessels can temporarily store energy.

Capillaries are small and numerous, and consist of just a single layer of endothelial cells. Nearly all cells in the body are within at least 10µm of a capillary. They are the main site of nutrient and gaseous exchange.

Venules and veins have relatively thin walls and may have valves to prevent blood flowing backwards. They have a large cross-sectional area and therefore a low resistance. They hold about 2/3 of the blood and some veins can contract. Venoconstriction aids venous return, thereby helping maintain cardiac output.

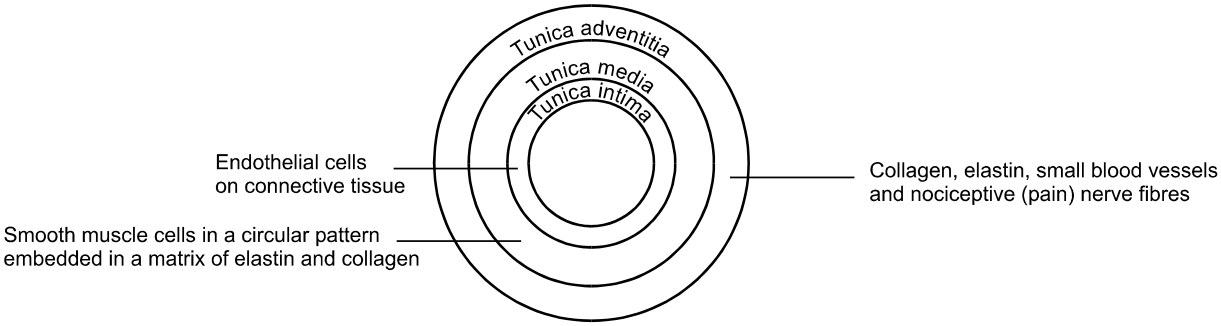

Figure 6. General structure of blood vessels

1.5. The fetal circulation

Within the womb, the supply of oxygenated fetal blood is dependent on the placenta rather than on pulmonary ventilation. In contrast to pulmonary ventilator processes, mechanisms within the placenta to increase oxygen delivery to the fetus are limited. Some specific adaptations to fetal life is the capacity of the fetus to bind greater concentrations of oxygen in its haemoglobin, by having fetal haemoglobin. The fetus also relinquishes this bound oxygen to the fetal tissues at lower oxygen tensions. The P_{50} is the partial pressure of oxygen at which 50% of haemoglobin is saturated with oxygen. The fetal oxygen-haemoglobin dissociation curve is shifted to the left of the maternal curve, thereby having a lower P_{50} value (Figure 7).

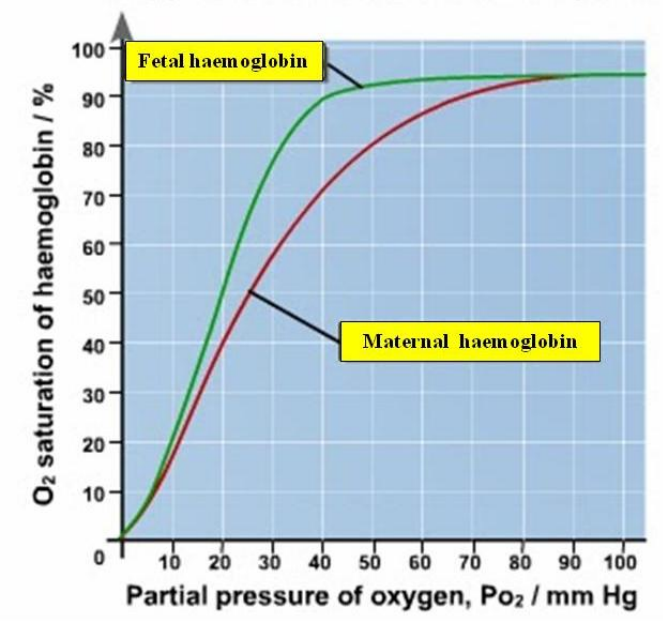

Figure 7. The maternal and fetal oxygen dissociation curve for haemoglobin

The fetus also has shunts in its circulation and preferential streaming ensures an adequate supply of oxygenated blood to tissues most at risk of hypoxic damage, like the brain. The fetal shunts are the *ductus venosus, foramen ovale* and *ductus arteriosus*. The *ductus venosus* shunts richly oxygenated blood coming from the placenta to the fetal heart, bypassing most of the fetal liver circulation. Oxygenated blood from the placenta travels through the umbilical cord to the right atrium of the fetal heart. As the fetal lungs are non-functional at this time from a gas exchange point of view, it is more efficient for the blood to bypass them. This is accomplished through further cardiac shunts. The *foramen ovale* shunts blood from the right atrium to the left atrium. The *ductus arteriosus* shunts blood from the pulmonary artery to the descending aorta.

Lecture 2. Cardiac function

2.0. The cardiac cycle

The cardiac cycle represents all of the events associated with blood flow through the heart during one complete heartbeat. Blood is pumped through the four chambers of the heart in strict cyclical sequence. After the ventricles (left and right) contract (*systole*) synchronously there is a period where the whole heart relaxes (*diastole*), during which the ventricles refill. The atria (left and right) then contract together providing the ventricles with more blood. The ventricles then contract without any delay (Figure 8).

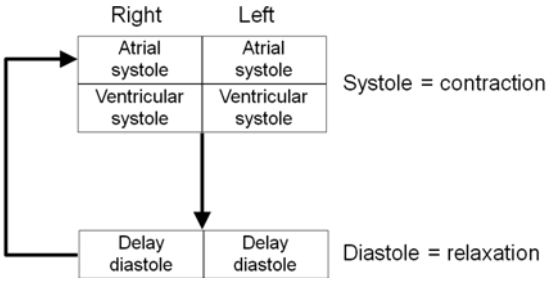

Figure 8. Events in the cardiac cycle

Analysis of the mechanical and electrical events in the cardiac cycle can give insight to defects of the heart valves, so it is important to consider them in detail. As the events are cyclical, one can pick any stage to start, but most books refer to the cardiac cycle as having 5 phases. Please refer to Figure 9 as we go through the cardiac cycle in detail.

Phase 1 - Atrial systole

Although most of the blood enters the ventricles while the atria are relaxed, the last 20% of filling is accomplished when the atria contract (atrial systole), opening the AV valves and forcing additional blood into the ventricles. When heart rate increases, as during exercise, atrial contraction plays a significant role in ventricular filling. The additional flow of blood is called the **atrial kick or boost**. When the atria contract, a small amount of blood is forced backwards into the venae cavae because there are no one-way valves to prevent backflow, although the opening of the veins do narrow during contraction. This retrograde movement can be seen as a pulse in the jugular vein of a normal person who is lying with the head and chest elevated about 30%. Interestingly, an observable jugular pulse higher on the neck of a person sitting upright is a sign that pressure in the right atrium is higher than normal.

Phase 2 – Isovolumetric contraction

As its name suggests, this is ventricular contraction without any change in ventricular volume. Ventricular systole begins as the spiral bands of ventricular muscle contract and squeeze the blood upwards. Blood pushing on the underside of the AV valves forces them closed so that blood cannot flow back into the atria. With both sets of AV and semilunar valves closed, the blood in the ventricles has nowhere to go. As a result pressure builds up quickly in the ventricles without changing ventricular volume.

Phase 3 – Ventricular ejection

As the ventricles contract, they generate enough pressure to open the semi-lunar valves: the aortic valve in the case of the left ventricle; the pulmonary valve in the case of the right ventricle. Blood is ejected into the arteries and the pressure generated by the ventricles becomes the driving force for blood flow. High-pressure blood is forced into the arteries, displacing the low-pressure blood that fills them and pushing it farther into the vasculature. Ventricular blood enters the aorta faster that it can leave the arterial tree, hence arterial pressure rises and the large elastic arteries become distended and engorged with blood.

Phase 4 – Isovolumetric relaxation

At the end of ventricular ejection, the ventricles begin to relax, leading to a rapid fall in ventricular pressure. As ventricular pressure falls below aortic pressure, a small amount of blood flows backwards and closes the aortic valve, giving a brief rise in arterial pressure, known as the *dicrotic notch*. The final third of ventricular blood flows away from heart, against a pressure gradient, due to *kinetic energy* - momentum. The overall change in ventricular volume during phases 3 and 4 of the cardiac cycle is a measure of the stroke volume.

Phase 5 – Late diastole

Both sets of chambers are relaxed and the ventricles begin to fill with blood passively before atrial systole and the beginning of a new cycle.

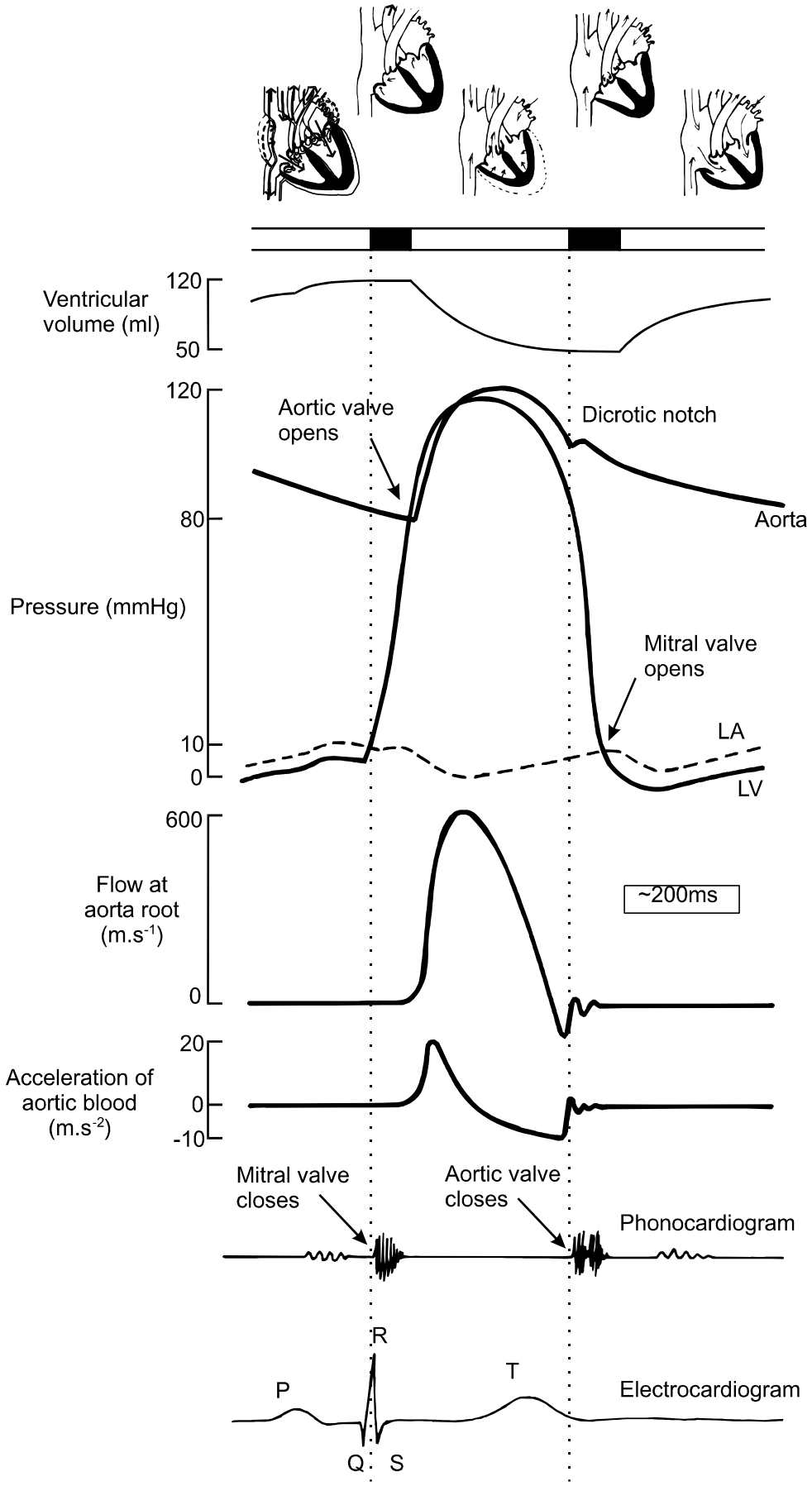

Figure 9. Events of the cardiac cycle in a resting subject

2.1. The phonocardiogram

The simplest direct assessment of heart function is listening through the chest wall, a process known as auscultation (*auscultare*; to listen to). Normally, there are two audible sounds. The first 'lub' is associated with closure of the AV valves. The second 'dub' with closure of the semi-lunar valves, in similar fashion to the sound made by 'slamming doors'.

Today, auscultation is usually performed through a stethoscope placed against the chest and the back of a person or animal. In certain abnormal conditions, additional sounds may become audible. A third sound may be heard and because of their timing they are called gallops: 'lub-dup-dup' or 'lub-lub-dup'. Other abnormal sounds include clicking, caused by abnormal movement of the valves, and murmurs caused by the 'whoosh' of blood leaking through an incompletely closed valve – valvular incompetence.

2.2. The ECG

Small changes in potential can be detected between different locations on the skin. These potentials are caused by the spread of electrical currents flowing through underlying structures. For instance if two electrodes are placed about two centimetres apart over the biceps a burst of electrical activity can be recorded when the muscle is contracted (this is called an EMG - electromyogram). Similarly if electrodes are placed on the skull potentials can be recorded that relate to neuronal activity (EEG - electroencephalogram). Electrodes placed on the eye can detect neuronal activity resulting from light flashes (electroretinogram).

Electrocardiography (ECG or sometimes EKG) is a process whereby small potentials (~1mV) are recorded between different locations on the skin that reflect the underlying activity of the heart (extracellular currents flowing around myocytes). These recordings were first made by William Einthoven & Augustus Waller in 1909. The ECG can be assessed as the electrical events are coupled to the mechanical events in the cardiac cycle (Figure 9).

There are two major components of an ECG: waves and segments. Waves appear as deflections above and below baseline. Segments are sections of baseline between two waves. In a healthy subject, there are three main waves on a normal ECG. The first wave, **P wave**, corresponds to atrial depolarisation. The next trio of waves is known as **the QRS complex**, and represents ventricular depolarisation. The final wave, the **T wave**, represents ventricular repolarisation. Atrial repolarisation is not represented as it is masked by the QRS complex.

The R-R interval is an accurate measure of heart rate. One interesting condition that can sometimes be observed on an ECG is a long Q-T interval. Long Q-T syndrome are most of the time inherited channelopathies, in wich mutations occur in myocardial Na^+ and K^+ channels. However, sometimes a long Q-T interval can occur because of side-effects from drugs. One well publicised incident involved a patient taking a non-sedating antihistamine called *Seldane* that binds to K+ repolarisation channels. After at least 8 deaths were attributed to the drug, the antihistamine was removed from the market!

2.3. Cardiac pressure-volume loops

Another way of representing the cardiac cycle is by plotting the changes in pressure against the changes in volume to form a cardiac pressure-volume loop (Figure 10).

The cycle begins at Point A. The ventricle has completed a contraction and contains the minimum amount of blood that will hold during a cardiac cycle. It is relaxed and hence its pressure is also at a minimum. For the left ventricular loop, blood is flowing into the atria from the pulmonary veins. Once pressure in the left atrium exceeds the pressure in the left ventricle, the mitral valve opens. Blood now flows into the left ventricle increasing its volume. As blood flows in, the relaxing ventricle expands to accommodate the volume. Consequently, volume increases with no change in pressure. The last portion of ventricular filling is completed by atrial systole (see above). The ventricle now contains the maximum volume of blood that it will hold during the cardiac cycle (Point B). Because maximal filling occurs at the end of ventricular relaxation, this is called the **end diastolic volume (EDV)**.

When ventricular contraction begins, the mitral valve closes. With both AV and semilunar valves closed, ventricular pressure increases dramatically without a change in volume – isovolumetric contraction – to reach Point C on the loop. Once ventricular pressure exceeds aortic pressure, the aortic valves open and ejection takes place. As a result, there is a rapid fall in ventricular volume to reach Point D. The heart does not empty itself completely of blood each time the ventricle contracts. The amount of blood left in the heart at the end

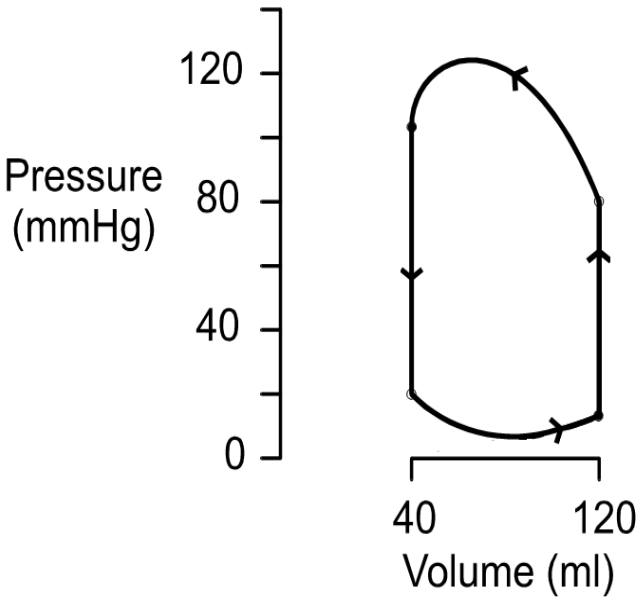

Figure 10. The heart pressure-volume loop

of ventricular contraction is known as **end systolic volume (ESV)**. The width of the loop represents the difference between EDV and ESV, which is by definition the stroke volume (SV). The area within the loop is the ventricular stroke work. At the end of ventricular contraction, the heart begins to relax. As a result, there is a rapid fall in pressure without a change in volume – isovolumetric relaxation – back to point A.

In *aortic stenosis*, left ventricular emptying is impaired because of high outflow resistance caused by a reduction in the valve orifice area when it opens. This high resistance causes a large pressure gradient to occur across the aortic valve during ejection, such that the peak systolic pressure within the ventricle is greatly increased. It also leads to an increase in the force opposing ventricular emptying – cardiac afterload, a decrease in stroke volume, and an increase in end-systolic volume. This leads to an increase in cardiac muscle mass, an enlarged heart and an increased risk of heart failure.

2.4. Intrinsic regulation of cardiac output

The contractility of the heart is dependent upon the degree to which the myocytes are stretched. The greater the stretch, the greater the force of contraction. This phenomenon was first described in experiments in the isolated frog's heart by Otto Frank in 1829 and later on in experiments in the isolated dog's heart by Ernest Starling. The isolated heart preparation permits us to observe intrinsic factors, which affect stroke volume regulation independent of innervation or endocrine (hormone) effects on the heart. Starling and his group performed two classical experiments.

Experiment 1 - Increased preload and the Starling Law

Under normal conditions, during the cardiac cycle, the amount of blood left at the end of the cardiac filling phase is called the **end diastolic volume (EDV)** and that at the end of the ejection phase, the **end systolic volume (ESV).** Let's consider what happens if peripheral resistance (**afterload**) and heart rate are maintained constant and cardiac filling pressure (**preload**) is increased. Under these conditions we find that cardiac output is increased. Because the heart is paced at constant rate, this increase in cardiac output is solely due to an increase in stroke volume. As you would expect **left ventricular and aortic pressures** also increase as a consequence of a greater amount of blood being ejected against the same resistance. The increase in filling pressure causes the ventricles to stretch increasing **end diastolic volume** (the amount of blood in the left ventricle just prior to ejection (Figure 11). This stimulates an **intrinsic** property of skeletal muscle, which is to increase the force of contraction in response to elongation or stretch. In the heart, this property of skeletal muscle is known as the **Frank-Starling mechanism** since it arose from a combination of the experiments by Frank and Starling. In 1915, Starling stated the following law: "**that the energy of contraction is a function of the length of the muscle fibre",** coining his famous **Starling Law of the Heart.**

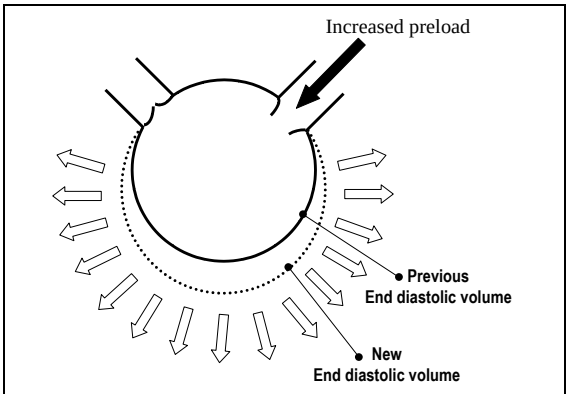

Figure 11. Effect of increased preload on cardiac output

Experiment 2 - Increased afterload and the Starling Law

Let's examine now the effect of another intervention on stroke volume. This time heart rate and filling pressures are maintained constant and peripheral resistance (**afterload**) is increased. This means that the heart finds it harder to force blood through the system. As a result, there is an increase in **aortic** and **left ventricular** pressures. As the heart is pumping against an increased resistance, stroke volume, and therefore cardiac output, fall initially. This transient fall in stroke volume is due to a less complete emptying of the ventricles during the ejection phase of the cardiac cycle producing an increase in **end systolic volume** (Figure 12). However, an increased afterload will also promote an increase in **end diastolic volume.** This will stretch the walls of the ventricles and increase cardiac output by the Frank-Starling mechanism (as we have seen before). Thus, during increased afterload there is a bi-phasic response in cardiac output. First, there is a decrease in cardiac output (for one or two beats) and then there is a recovery of cardiac output.

2.5. The Anrep effect

The Anrep effect, named after Russian physiologist Gleb von Anrep, is an autoregulation method in which myocardial contractility increases with afterload. Sustained myocardial stretch activates tension dependent Na+/H+ exchangers, bringing Na+ ions into the sarcolemma. This increase in Na+ in the sarcolemma reduces the Na+ gradient exploited by sodium-calcium exchanger (NCX) and stops them from working effectively. Ca2+ ions accumulate inside the sarcolemma as a result and are uptaken by sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) pumps. Calcium induced calcium release (CICR) from the sarcoplasmic reticulum is increased upon stimulation of the cardiac myocyte by an action potential. This leads to an increase in the force of contraction of the cardiac muscle to try and increase stroke volume and cardiac output to maintain tissue perfusion.

2.6. Extrinsic regulation of cardiac output

The heart is innervated with parasympathetic and sympathetic branches of the autonomic nervous system. These provide extrinsic influences on its rate and force of contraction. Both branches originate from the **cardio-vascular centre** in the medulla oblongata.

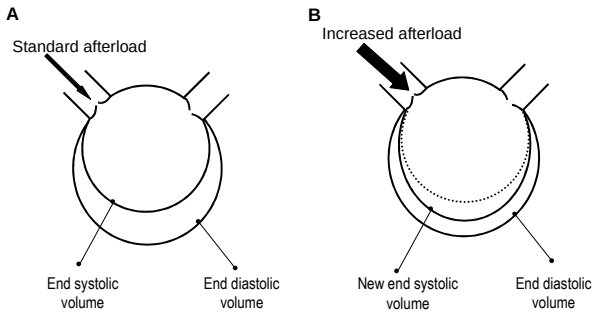

Figure 12. Effect of increased peripheral resistance (afterload) on cardiac output

Sympathetic influences

From the thoracic region of the spinal cord **cardiac accelerator nerves** extend out to the **sino-atrial (SA) node**, **atrio-ventricular (AV) node** and most portions of the myocardium. Impulses in the cardiac accelerator nerves release **noradrenaline**, which binds to β_1 receptors on cardiac muscle fibres. At the SA node this increases frequency of contraction (**positive chrono-tropic effect**)**.** At contractile fibres in the ventricles noradrenaline increases contractility (**positive inotropic effect**).

Parasympathetic influences

Parasympathetic nerve inpulses reach the heart via the right and left **vagus (X) nerves.** They release **acetylcholine**, which acts on muscarinic receptors at the SA and AV nodes and on the atrial myocardium. Acetylcholine reduces heart rate (**negative chronotropic effect**) but has little or no effect on contractility of the ventricles in most species.

Endocrine influences

Some hormones have both chronotropic and inotropic effects. Of these the most common is adrenaline released from the medulla of the adrenal gland. Adrenaline also acts on cardiac β_1 receptors to increase frequency and force of contraction, maintaining neurally-mediated sympathetic effects.

2.7. Pacemaker potential

The initial membrane potential of the SA node cell is only about -60mV, and it depolarises spontaneously. This slowly increasing potential is called the 'pacemaker potential'. When it reaches threshold, at ~ -40 mV in nodal cells, it triggers an action potential, which sparks off the next heartbeat. Thus, the **slope** of the pacemaker potential is very important as it determines the time taken to reach threshold value. Sympathetic influences increase the slope and therefore increase heart rate; parasympathetic decrease it and therefore decrease heart rate.

Lecture 3. Haemodynamics

3.0. Why does blood flow?

If you ask people why blood flows through a cardiovascular system, many of them respond, 'So that oxygen and nutrients can get to all parts of the body.' Although, this is true, it is a teleological answer, one that describes the purpose of flow rather than the mechanism. A simple mechanistic answer is that liquids flow down pressure gradients from regions of high pressure to regions of low pressure, ie. They obey the law of fluids derived by Darcy, and this can be illustrated as in Figure 13.

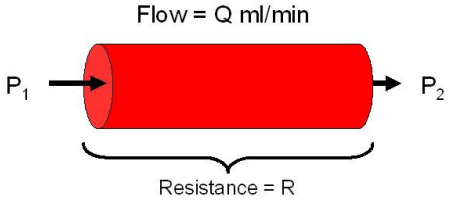

Figure 13. Darcy's law

Darcy's law of flow is really the hydraulic equivalent of Ohm's Law of electricity. Darcy's law was formulated in 1856 following his study of water flowing through gravel beds of the fountains of Dijon! The law states that flow (Q) in the steady state is linearly proportional to the pressure difference between two points, $\Delta P = (P_1 - P_2)$ and inversely proportional to resistance (R). So:

$$Q = \frac{\Delta P}{R}$$

One can apply this law to the cardiovascular system, as in the circulation the flow of blood to any organ is driven by the pressure difference between the arteries that supply the region in question and the veins that drain it. This is called the perfusion pressure (ΔP, or $P_A – P_V$). The resistance in the circulation is called the vascular resistance, and it is inversely proportional to blood flow. So, in the cardiovascular system:

$$\text{Blood flow} = \frac{\text{Perfusion pressure}}{\text{Vascular resistance}}$$

Blood flow is determined by cardiac output and perfusion pressure is almost equal to arterial blood pressure as pressure in the venous system is only a few mmHg, so another representation of the equation would be:

$$\text{Cardiac Output} = \frac{\text{Blood pressure}}{\text{Vascular resistance}}$$

The equation states that cardiac output is proportional to arterial blood pressure, but inversely proportional to vascular resistance.

3.1. Determinants of arterial blood pressure and vessel resistance

So, in the simplest terms, one can say that arterial blood pressure is determined by cardiac output and vascular resistance. In turn, cardiac output is determined by the amount of blood pumped out of each ventricle per beat, i.e. the **stroke volume** (SV), and how fast it is being pumped out, i.e. the **heart rate** (HR). So, the equations below summarise the main determinants of arterial blood pressure:

$$\text{Blood pressure} = \text{Cardiac Output} \times \text{Vascular Resistance}$$

$$\text{Cardiac Output} = \text{Stroke volume} \times \text{Heart rate}$$

But what determines vascular resistance? In an ideal system, a substance in motion would remain in motion. However, no system is ideal as movement causes friction. Just as a ball rolled across the ground loses energy to friction, blood flowing through the blood vessels encounters friction from the walls of the vessels. In fact, the flow of liquid through a tube can be thought of as parallel streams. The stream directly next to the vessel wall is the slowest because of the greatest friction and subsequent layers slide past at increasing velocities. Unsurprisingly, the maximum velocity occurs at the centre of the tube. For a Newtonian fluid, such as water, the velocity profile is a parabola and the pattern produced is called laminar flow (Figure 14). Blood flowing through the blood vessels can also be thought of as laminar, but the profile relative to water is blunter.

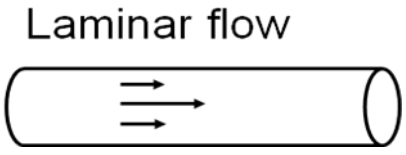

Figure 14. Laminar flow

We know that blood pressure is highest in the arteries and decreases continuously as blood flows through the vascular tree (Figure 16). Is wall friction wholly responsible for this? No, because in addition to wall friction, resistance

to laminar flow can be influenced by 3 components: the radius of the tube (r), the length of the tube (L) and the viscosity (thickness) of the fluid (η, the Greek letter eta). The following equation, derived by the French physician Jean Leonard Marie Poiseuille and known as Poiseuille's Law, shows the relationship between these factors:

$$R \propto \frac{L\eta}{r^4}$$

L = length of vessel
η = viscosity of blood
r = radius of vessel

The equation shows that: (1) the resistance to fluid flow offered by a tube increases as the length of the tube increases, (2) resistance increases as the viscosity increases, but (3) resistance decreases as the tube's radius increases. To help you remember these relationships, think of drinking through a straw. You do not need to suck as hard on a short straw compared to a long one (the resistance offered by the straw increases with length). Drinking water through a straw is easier than drinking a milkshake (resistance increases with viscosity). And dinking the milkshake through a big fat straw is much easier than through a skinny cocktail straw (resistance increases as radius decreases).

What are the partial contributions of length, viscosity and radius in altering vascular resistance in the circulation? Well, the length of the circulation in different species is determined by the anatomy of the system and, hence, it is essentially constant. However, to illustrate the point we may think of the resistance to flow in the capillaries. Capillary beds have a relatively low resistance despite their small radius. This is partly because they are short, most of them < 1mm, but also because many of them are connected in parallel (Figure 15). These vessels have a huge cross-sectional area, resulting in low velocity giving time for diffusion, which is useful as they are the main site for exchange.

Blood viscosity is determined by the ratio of red blood cells to plasma, which can be calculated by the **haematocrit**, a percentage (Figure 16). Normally, viscosity is constant. However, increases in haematocrit occur with residence at high altitude and decreases in haematocrit can occur due to anaemia.

Fåhræus–Lindqvist effect

This is an effect where the viscosity of a fluid, in this case blood, changes with the diameter of the tube it travels through. In particular there is a decrease of viscosity as the tube's diameter decreases (only if the vessel diameter is between 10 and 300 micrometers).

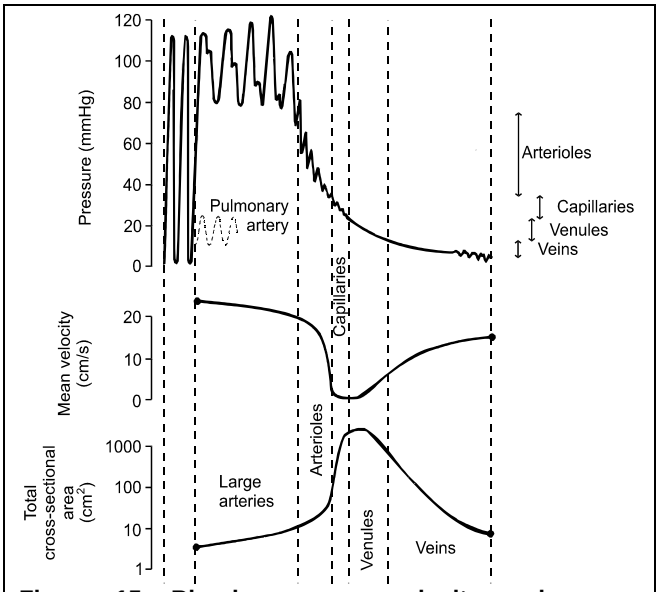

Figure 15. Blood pressure, velocity and cross-sectional area along the systemic circulation of man from left ventricle to vena cava. Arrows on the right of the figure show the pressure drops. Note the low pressure in the pulmonary artery, large pressure drop across the arterioles and the large cross-sectional area of the capillaries and venules. [Modified from Levick]

This is because erythrocytes move over to the centre of the vessel, leaving plasma at the wall of the vessel. The effect can be explained by the concept of a **plasma cell-free layer**, a thin layer adjacent to the capillary wall that is depleted of red blood cells. Because the cell-free layer is red cell-poor, its *effective* viscosity is lower than that of whole blood. This layer therefore acts to reduce resistance to blood flow within the capillary and helps maintain arterial pressure homeostasis.

3.2. Role of the radius in determining resistance

By far, the variable that affects vascular resistance the most is vessel radius. If we consider only resistance (R) and the radius (r) from Poiseuille's Law, the relationship between them can be expressed as $R\alpha 1/r^4$. The effect of radius can be illustrated by considering Figure 17, below:

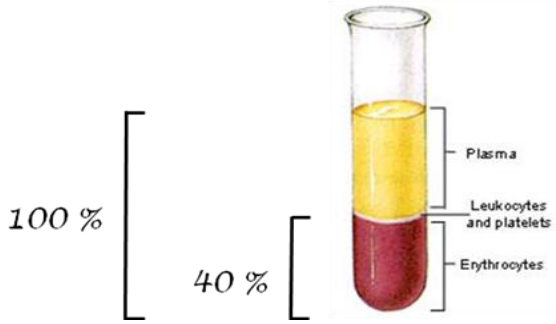

Figure 16. Calculation of haematocrit

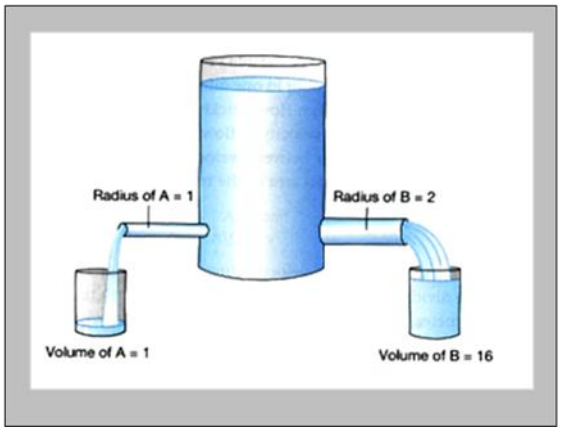

Figure 17. Radius and resistance

In tube A, with a radius of 1, its resistance is proportional to $1/1^4$ or 1. In tube B, with a radius of 2, the resistance offered is $1/2^4$ or $1/16^{th}$ of tube A. Because flow is inversely proportional to resistance, flow increases 16 fold when the radius doubles. As you can see from this example, a small change in radius of a tube has a dramatic effect on the flow though the tube. Similarly, a change in the radius of a blood vessel will have significant consequences on blood flow and vascular resistance. From Figure 16, one can see that the greatest reduction in pressure occurs as blood flows though the arterioles, which are infamous for being able to change their diameter and are sometimes referred to as the 'taps' of the circulation. Changes in vessel diameter are referred to as vasomotion; a decrease in diameter is known as vasoconstriction and an increase as vasodilatation. In the circulation, vasomotion can be affected by nerves, hormones and local factors.

3.3. Nerves and hormones affecting vasomotion

You will discuss the autonomic nervous system in the future in detail. For now, it is sufficient to say that it consists of two arms, the sympathetic nervous system and the parasympathetic nervous system. Sympathetic nerves (Figure 18) are characterised by having a short pre-ganglionic fibre and a long post-ganglionic fibre, where the pre-ganglionic neurotransmitter is acetylcholine (Ach) and the postganglionic neurotransmitter is noradrenaline (NA). Total peripheral vascular resistance is largely regulated by the sympathetic nervous system, which contains mostly vasoconstrictor nerves. Vasoconstrictor nerves are **tonically** active imposing a constant squeezing 'tone' on vessels which maintains total peripheral resistance and, thus, arterial blood pressure. However, the tone of a blood vessel can be increased further by decreasing its radius due to vasoconstriction. This may occur as a result of an action potential stimulating a sympathetic fibre, which travels to the synapse containing vesicles with the stored neurotransmitter - noradrenaline (NA). Noradrenaline acts on receptors on blood vessels to cause vasoconstriction.

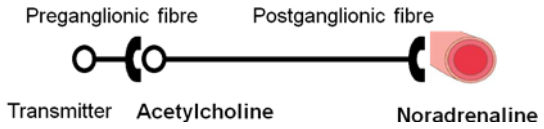

Figure 18. Sympathetic nerves

Both arterioles and venules are innervated by sympathetic vasoconstrictor fibres, except that arterioles are much more innervated than venules. The result of an increase in constriction of the arterioles is an increase in total peripheral vascular resistance and an increase in arterial blood pressure. The result of an increase in constriction of the venules is a faster return of blood to the heart or an increase in venous return.

By far the most efficient mechanism to dilate a blood vessel is to withdraw or inhibit sympathetic 'tone', as this increases vessel radius, promoting vasodilatation.

Previously, we have discussed that the circulation is responsible for the transport of hormones, which are chemicals produced and secreted into the bloodstream by an endocrine gland. The classic hormone adrenaline has important vasoactive properties, as it constricts some circulations and dilates others. For instance, during a physiological stress, such as during whole body exercise, large amounts of adrenaline will be secreted into the bloodstream. In most peripheral circulations, adrenaline may cause vasoconstriction, which will help maintain arterial blood pressure. However, in skeletal muscle, adrenaline may actually cause dilatation. In this way, the differential effects of adrenaline on various circulations will redistribute the cardiac output to the areas, which require the greatest delivery of oxygen and nutrients.

3.4. Local factors: Nitric oxide

A chance observation almost two decades ago led to the discovery that the **endothelium** itself plays a key role in promoting changes in peripheral vascular tone. Furchgott and Zawadski discovered in 1980 that the vasodilator arterial response to acetylcholine

changed to a vasoconstrictor response if the endothelial lining was rubbed away. The explanation is that the vasodilator effects of acetylcholine are indirect. Acetylcholine stimulates the endothelium to produce a substance that causes vasodilatation. Thus when the endothelium is absent no vasodilatation is achieved. This substance was first known as **endothelium derived relaxation factor (EDRF)** but it is now known to be the same as **nitric oxide (NO)**.

Nitric oxide is not stored. Its formation is stimulated by substances that activate endothelial cells, such as acetylcholine. When stimulated, NO is produced by cleavage from the amino acid arginine by an endothelium membrane enzyme called **NO synthase**. The activity of this enzyme is regulated by the level of intracellular Ca^{2+}-calmodulin complex, so that agents that promote extracellular Ca^{2+} entry into endothelial cells (e.g. acetylcholine) increase the rate of NO synthesis (Figure 19).

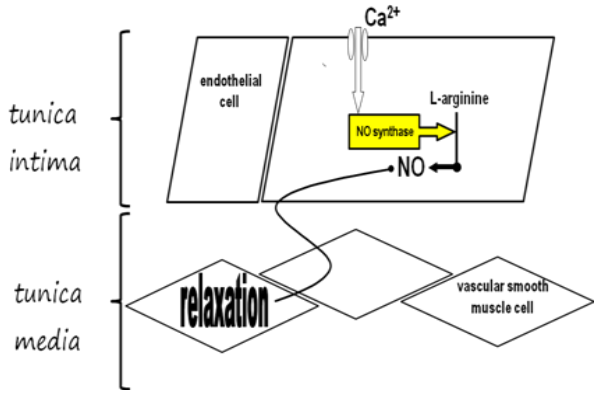

Figure 19. Synthesis of nitric oxide

3.5. Measuring blood pressure

It is important to maintain arterial blood pressure within a physiological range. Arterial blood pressure can be estimated by use of a sphygmomanometer, an instrument consisting of an inflatable cuff and a pressure gauge. The cuff encircles the upper arm and is inflated until it exerts pressure higher than the pressure driving arterial blood. When cuff pressure exceeds arterial pressure, blood flow in the lower arm stops (Figure 20 A). Now pressure in the cuff is gradually released. When the cuff pressure falls below sys-tolic arterial pressure, blood begins to flow again. As blood squeezes through the still-compressed artery, a thumping noise called a Korotkoff sound can be heard with each pressure wave (Figure 20 B). Once the cuff pressure no longer compresses the artery, the sound disappears (Figure 20 C). The pressure at which the Korotkoff sound is first heard represents the highest pressure in the artery and is recorded as the systolic pressure. The point at which the Korotkoff sound disappears is the lowest pressure in the artery and is recorded as the diastolic pressure. By convention, systolic is written over diastolic pressure, and it is for most of you, around 120/80 mmHg. Mean arterial blood pressure (MAP) is calculated as the diastolic (D) plus a third of the difference between systolic (S) and diastolic (D) blood pressure:

$$MAP = D + \frac{1}{3}(S-D)$$

3.6. Arterial stiffness

This is a measure of the rigidity of your blood vessels. With ageing and with disease, vessels deposit calcium and collagen, making them rigid. Analysis of blood pressure waveforms provides data on arterial stiffness, workload on the heart and risk of heart disease. An increase in pulsatility may be calculated by an increase in the systolic to diastolic pulse (SD ratio) or as an increase in the pulsatility index PI (S-D/mean). Circulations with increased PI signify increased vascular resistance.

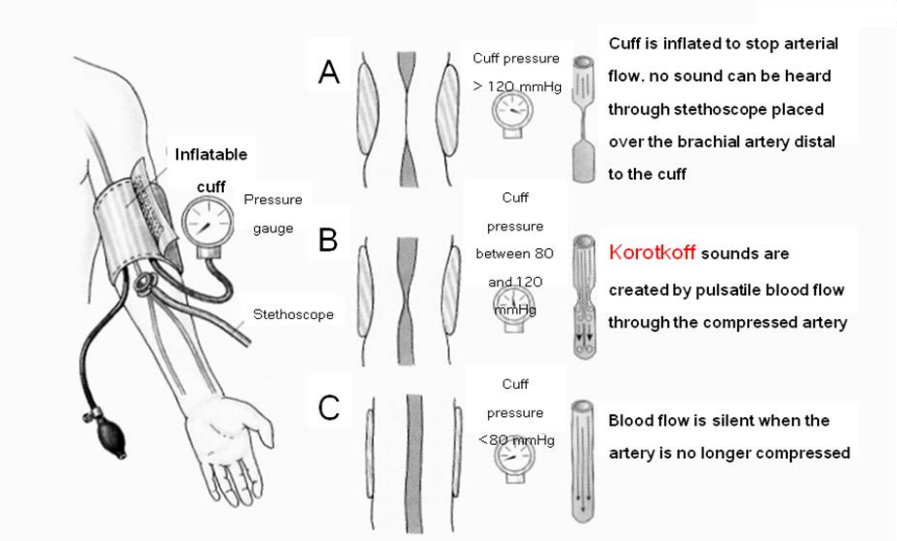

Figure 20. Measurement of blood pressure

Lecture 4. Integration of reflex control

4.0. Reflex arcs

To the physiologist, the simplest model of a reflex arc is one that is composed of a **sensor**, which sends information to the brainstem (**integrator)** via **afferent pathways**. The brainstem integrates the information and sends commands to **effector** organs via **efferent pathways** (Figure 21). Up to now, we have discussed neural and endocrine **efferent pathways**, which regulate arterial blood pressure by promoting changes in cardiac output and peripheral vascular resistance. This section will discuss the **sensors** and **afferent pathways** of the different reflex responses, which regulate arterial blood pressure. We will concentrate on **mechanoreceptors** and **chemoreceptors**.

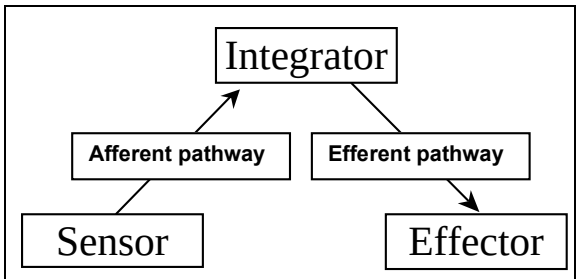

Figure 21. Reflex arc

4.1. Arterial baroreceptors

The arterial mechanoreceptors are usually referred to as the arterial **baroreceptors** since they respond to changes in arterial blood pressure. We have two types of arterial baroreceptors - the **carotid baroreceptors** and the **aortic baroreceptors**. The carotid group are present within the **carotid sinus** at the bifurcation of the internal and external carotid arteries. The aortic group are present in the **arch of the aorta** (Figure 22). Once the carotid baroreceptors are stimulated, they send **afferent** information (dotted lines) to the brainstem (medulla) via the **carotid sinus nerves**, which join onto the **glosso-pharyngeal (IXth cranial) nerve.** Similarly, the aortic baroreceptors send afferent information to the brainstem by the **aortic nerve**, which joins onto the **vagus (Xth cranial) nerve**. Note that the vagus nerve contains both **afferent** and **efferent** (solid lines) fibres.

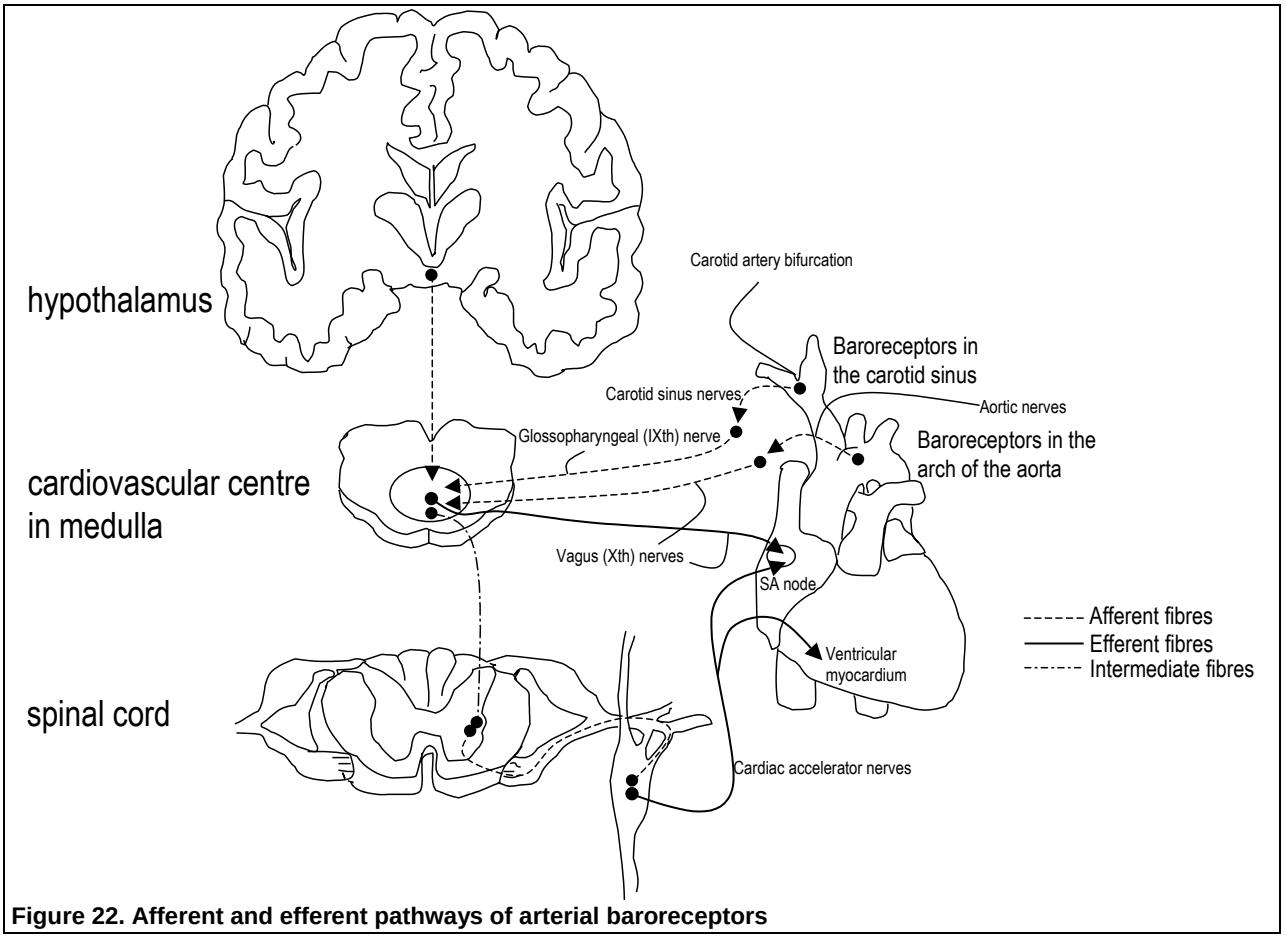

Figure 22. Afferent and efferent pathways of arterial baroreceptors

4.2. Carotid and aortic baroreflexes

Baroreceptor reflexes are present to restore arterial blood pressure back to normal once it is increased or decreased. This is important because a fall in arterial blood pressure (**hypotension**) will reduced perfusion of oxygenated blood to the tissues and an increase in arterial blood pressure (**hypertension**) can cause damage to fragile circulations, such as those perfusing the brain (**cerebral** circulation). Given the anatomical arrangement of the arterial baroreceptors, it is not surprising to find that there are two baroreceptor reflexes: the **carotid sinus reflex** and the **aortic reflex**. The carotid sinus reflex helps maintain normal pressure in the circulation perfusing the brain; the aortic reflex governs systemic arterial blood pressure homeostasis. The principle behind the physiology of the carotid sinus or aortic reflex is the same.

4.3. Physiology of baroreception

Baroreceptor fibres from the **carotid sinus** and **aortic arch** are tonically active. This means that they send continuous bursts of action potentials to the brainstem via their respective **afferent pathways** (see Figure 23). Tonic baroreceptor discharge is in phase with the arterial blood pressure (AP) pulse. Any increase in mean arterial blood pressure, say from 80 to 100 mmHg, stretches the wall of the aorta and carotid sinus, and the stretching stimulates the baroreceptors. When an individual baroreceptor fibre is stretched, the frequency of the action potentials it triggers in the afferent nerve is increased (Figure 23A). An increased rate of action potentials to the cardiovascular centre results in stimulation of

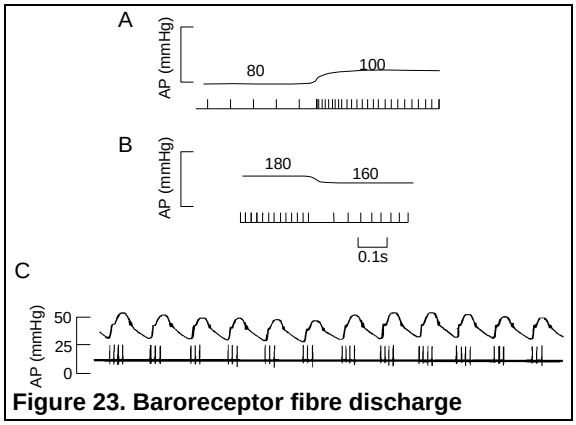

Figure 23. Baroreceptor fibre discharge

the cardiac inhibitory centre (which increases efferent parasympathetic discharge) and inhibition of the cardiac acceleratory centre (which reduces efferent sympathetic discharge). The end result is a decrease in heart rate and force of ventricular contraction, both of which lead to a fall in cardiac output and help restore arterial blood pressure (Figure 24). The objective of the cardiac baroreflex is potentiated by the vasomotor baroreflex. The increased rate of action potentials to the vasomotor centre results in reduced sympathetic impulses along sympathetic fibres, which cause peripheral vasoconstriction. The end result is a fall in both **arteriolar tone** and **venomotor tone**. The combined reductions in cardiac output and total peripheral vascular resistance help restore blood pressure back to normal. Conversely, a fall in arterial blood pressure, such as that resulting from a sudden loss of blood volume due to haemorrhage results is a decrease in the frequency of baroreceptor afferent discharge of both carotid and aortic baroreceptor fibres. The reflex responses are the opposite to the ones shown in Figure 24.

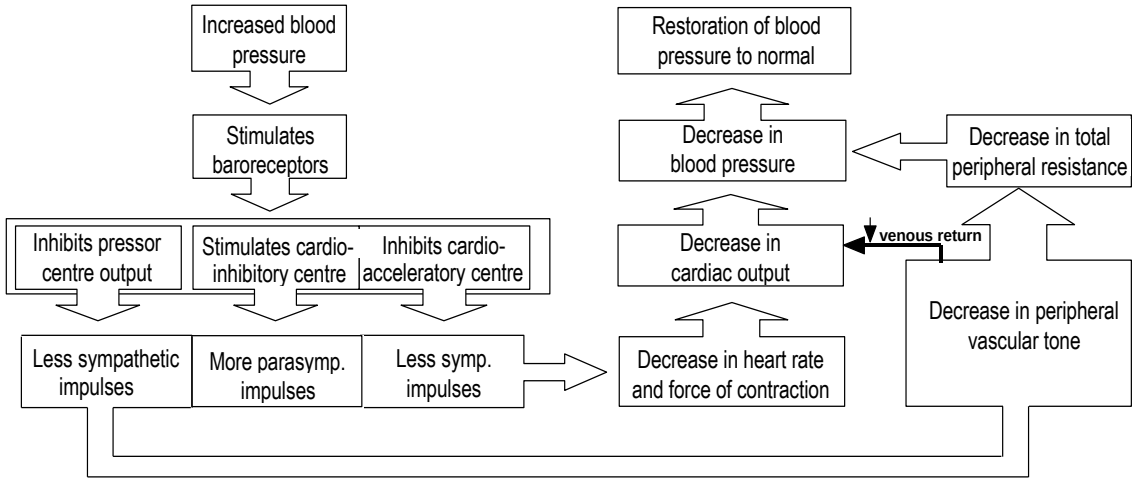

Figure 24. Cardiac and vasomotor baroreflexes

4.4. Sensitivity and setting of the arterial baroreflex

The sensitivity and setting of the baroreflex can be assessed by measuring the heart rate responses to controlled changes in arterial blood pressure. In human subjects, baro-receptor activity can be altered by injecting a vasoconstrictor drug, such as **phenylephrine**. Phenylephrine is the synthetic form of noradrenaline and, just like noradrenaline, acts on α_1-adrenergic receptors to cause peripheral vasoconstriction and, thus, an increase in arterial blood pressure. Increases in arterial blood pressure trigger a fall in heart rate by the cardiac baroreflex. Similarly, treatment with vasodilators, such as **sodium nitroprusside**, will cause a fall in blood pressure with corresponding increases in heart rate, via the cardiac baroreflex. From such experiments a stimulus-response curve can be constructed as shown in Figure 25.

The response proves to be a sigmoid function of the applied pressure change and, in the simplest of cases, the **maximum slope** (Δheart rate : Δ pressure) of the response curve can be used as calculation of the **sensitivity** or **gain** of the baroreflex. The pressure which the reflex strives to maintain can be called its **setting** or **set point**.

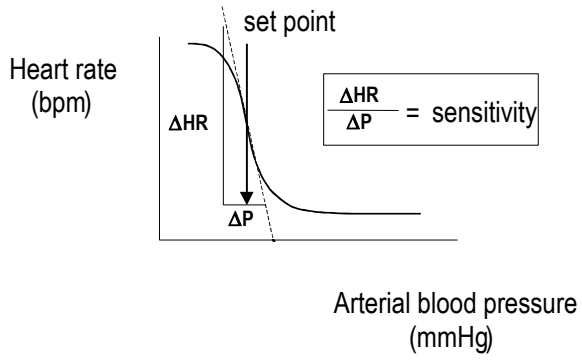

Figure 25. Baroreflex function curves

Central re-setting This occurs during the **defence reaction**. This is where the rise in arterial blood pressure is not accompanied by a fall in heart rate because the baroreflex is reset centrally to operate around a higher pressure. Stimulation of the **hypothalamus** '**gates out'** baroreceptor afferent information at the cardiovascular centre.

Peripheral re-setting When pressure is raised in a sustained manner, the **stimulus-response curve shifts** to the right so that the **set point** of the baroreflex changes (Figure 26). If this did not occur, the sustained increase in arterial blood pressure would lead to a sustained increase in baroreceptor discharge, which would use a lot of energy. The advantage of the shift to the right in the stimulus-response curve is that it allows a greater resting blood pressure without a sustained increase in baroreceptor discharge. A shift in the set point can also have disadvantages since it may give rise to clinical **hypertension**.

An example of **peripheral re-setting** occurs at birth when arterial blood pressure is changing from fetal to newborn levels. Resting arterial blood pressure in the fetus (~40 mmHg) is much lower than that measured post-natally (~60-80 mmHg). Peripheral re-setting shifts the **fetal set point** to the **post-natal set point**.

The **setting** of the baroreflex is not the only thing that changes from fetal to post-natal life. Blanco and colleagues in 1988 measured carotid baroreceptor discharge to imposed changes in arterial blood pressure in anaesthetised fetal sheep at different stages of gestation and in newborn lambs. They demonstrated that **baroreceptor sensitivity** also decreased with increasing age since the slope of the curves diminishes from fetal to post-natal life (Figure 27).

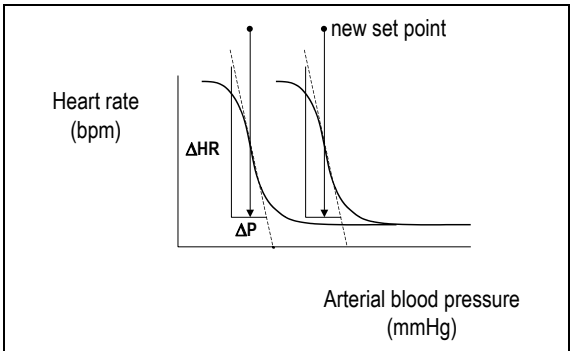

Figure 26. Peripheral re-setting of barorflex

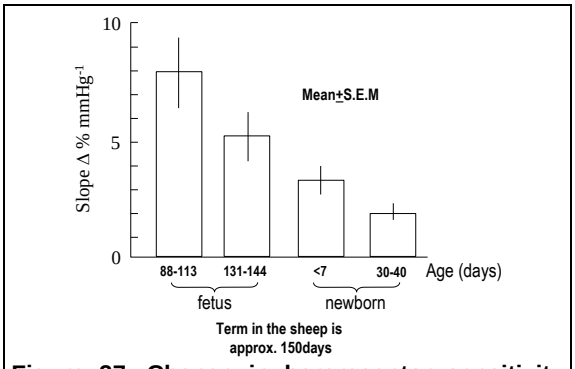

Figure 27. Change in baroreceptor sensitivity from fetal to newborn life

4.5.Atrerial chemoreceptors

Like the arterial baroreceptors, the arterial chemoreceptors are divided into the **carotid** and **aortic** chemoreceptors (Figure 29A). The **carotid** chemoreceptors send **afferent** fibres to the brainstem via the **carotid sinus nerves**, which join onto the **glossopharyngeal (IXth) nerve**. The **aortic** chemoreceptors send afferent fibres to the brainstem via the **aortic nerve**, which joins onto the **vagus (Xth) nerve** (see Figure 22).

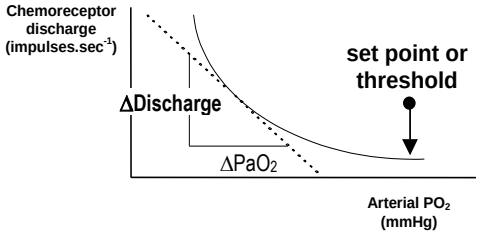

Figure 29. Chemoreflex function curve

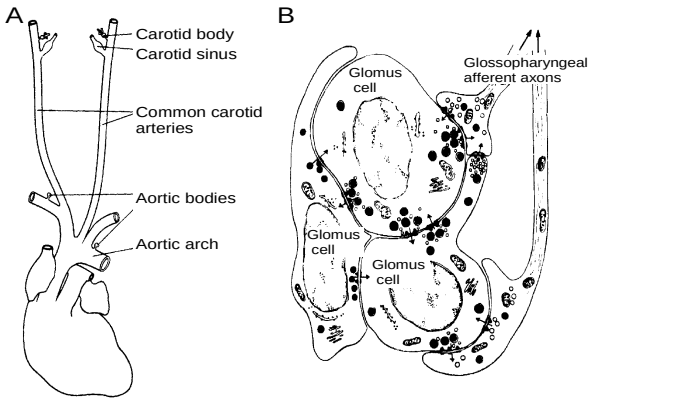

Figure 28. Anatomical arrangement of peripheral barorecptors and chemoreceptors (A) and the chemoreceptor glomus cell (B)

4.6. Physiology of chemoreception

Classically, peripheral chemoreceptor tissue is made of islands of Type I cells also known as **glomus cells** (Figure 28B). The glomus cells are the actual oxygen sensors and they are stimulated by a fall in partial pressures of oxygen (PO_2) in the arterial blood (PaO_2). They have lots of mitochondria and dark vesicles, which contain peptides needed for **chemotransduction**. A fall in PO_2 in the environment, such as that which results from ascent to high altitude, is known as **hypoxia**. Environmental hypoxia results in a fall in arterial PO_2 (PaO_2) which is referred to as **hypoxaemia**. When hypoxaemia occurs the discharge of both carotid and aortic chemoreceptors increases.

Figure 29 shows the relationship between arterial PO_2 and peripheral chemoreceptor discharge. The PO_2 at which peripheral chemoreceptor discharge starts is known as the chemoreceptor **threshold or set-point**. In a similar way to the physiology of the arterial baroreceptors, the **sensitivity** of the arterial chemoreceptors is determined by the slope of the relationship between PO_2 and chemo-receptor discharge.

4.7. Peripheral chemoreceptor re-setting

This refers to a shift of the peripheral chemoreceptor discharge curve towards a lower or higher PO_2. A classical example of peripheral chemoreceptor re-setting is also that which occurs during the transition from fetal to post-natal life. In contrast to the PO_2 of adult blood which is about 90-100 mmHg, the PO_2 of fetal blood is much lower, around 25-40 mmHg. Consequently the fetal chemo-receptors are 'set' at a very much lower PO_2 than chemoreceptor setting in the adult. Following birth, the peripheral chemoreceptor set point has to re-set to be able to be triggered at a higher threshold. The end result is that the adult chemoreceptor discharge curve shifts to the right (Figure 30). If the arterial chemoreceptors would not re-set from fetal to post-natal life, they would be silenced by the enriched partial pressure of oxygen in the extra-uterine environment. A fault in peripheral chemoreceptor re-setting from fetal to post-natal life may contribute to **cot death** (Sudden Infant Death Syndrome - SIDS).

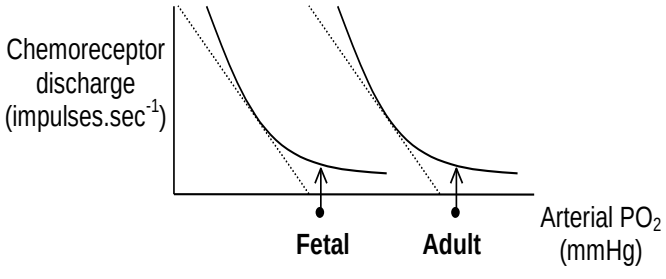

Figure 30. Re-setting of peripheral chemo-receptors before and after birth

4.8 Interaction between ventilation and cardiovascular chemoreflexes

In the adult, hypoxia elicits marked cardiovascular and ventilatory adaptive responses. The cardiovascular response involves an increase in heart rate and an increase in blood flow to most circulations including the brain, the heart and the adrenal glands. In the adult, hypoxia even promotes vasodilatation in peripheral circulations, such as the femoral circulations, which perfuse the hind limbs. In any circulation, vasodilatation may be expressed as an increase in blood flow or as a fall in in vascular resistance.

In 1962, Daly and Scott performed classical experiments, which revealed an important interaction between ventilatory responses and cardiovascular responses mediated by the peripheral chemoreceptors. In very simple terms, they induced hypoxia in dogs that were allowed to breathe either spontaneously or in dogs that were mechanically ventilated. In dogs, which breathed spontaneously hypoxia elicited an increase in ventilatory rate accompanied by an increase in heart rate and a decrease in femoral vascular resistance. However, in dogs in which their ventilation was controlled and, thus were not allowed to hyperventilate, hypoxia induced totally the opposite cardiovascular responses: a fall in heart rate and an increase in femoral vascular resistance (Figure 31).

Daly and Scott concluded that in the adult, hypoxia elicits **primary chemoreflex cardiovascular responses** (a fall in heart rate and an increase in peripheral vascular resistance), which become modified by hyperventilation to secondary chemoreflex cardiovascular responses (an increase in heart rate an a decrease in peripheral vascular resistance). During hyperventilation, stretch receptors in the lung increase their afferent discharge to the brainstem. This influences the cardiac and vasomotor centres to inhibit both vagal discharge to the heart and sympathetic outflow to the peripheral circulations. During **diving the adult mammal** shows the **primary chemoreflex** cardiovascular responses to hypoxia.

4.9 Fetal response to acute hypoxia

The fetus is not dependent on pulmonary ventilation for oxygenation since it obtains its oxygen from the mother via the placenta. Consequently, it makes sense that the fetus does not breathe while in the womb. But actually, the fetus does make breathing movements *in utero*, not to breathe but to practice pulmonary ventilation after birth. These breathing movements develop the intercostal muscles and the alveoli within the lungs. Hypoxia is a common challenge to the fetus during development and it may occur, for example, during compression of the umbilical cord. Interestingly, when the fetus suffers a hypoxic challenge it ceases to make breathing movements. This makes sense because breathing movements consume energy so inhibiting them is beneficial during a period of reduced oxygen supply, particularly since they are not needed for oxygenation. If the fetus does not hyperventilate during hypoxia, one would think that it must show the primary chemoreflex cardiovascular responses to hypoxia, like the diving adult. This is exactly what happens. During an episode of hypoxia, the fetus shows a marked reduction in heart rate and a marked increase in femoral vascular resistance. Thus, the **fetal cardiovascular responses to hypoxia** are another good example of the **primary chemoreflex cardiovascular response**s to hypoxia. For further reading see Giussani et al. *J Physiol*. 594(5): 1215-1230, 2016.

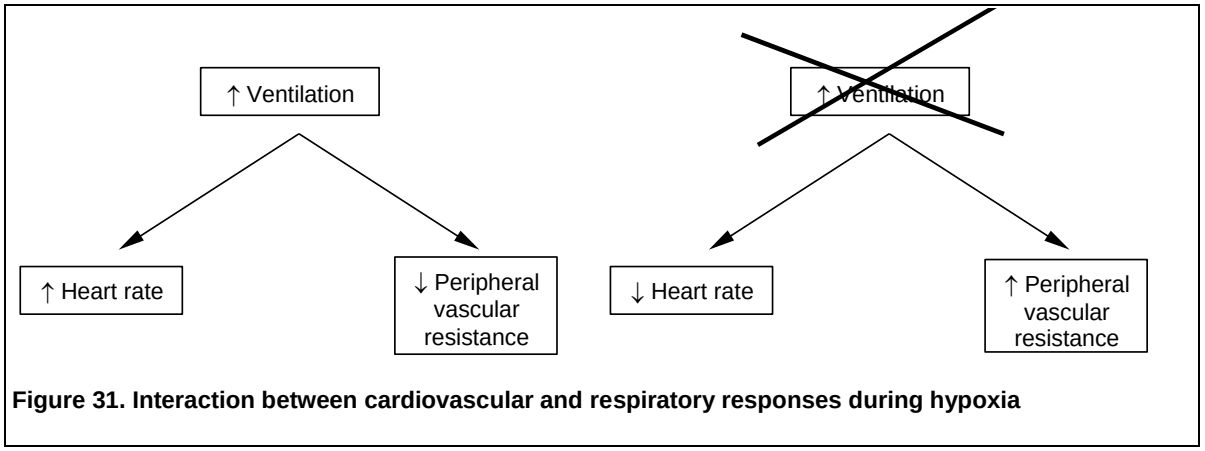

Figure 31. Interaction between cardiovascular and respiratory responses during hypoxia