

B18 Quantitative Physiology

Systems Physiology

4 Lectures, Hilary Term 2022

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1 examples sheet B18

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1 Introduction

1.1 Context within B18 course

Previously in B18 we concentrated on physiology at the cellular level. Now we move to the macro scale and consider how the concepts we have met play out in the whole body and the various systems within it. Inevitably, this is highly selective and there are many other very important body systems that we will not have time to consider; however, hopefully the ideas that we introduce here will help you in your exploration of these other systems.

1.2 Snippet lectures on Canvas

The online pre-recorded lectures closely follow the notes in terms of content and are delivered in short ~20-minute snippets to enable easy reference. The table below shows the contents and the related online quizzes aimed at consolidating the material taught in the snippets.

Snippet	Title	Notes
0	Introduction, welcome, context	
1	Compartment models – one compartment	
2	Compartment models – two compartments	
	Quiz 1	
3	Heart introduction	
4	Cardiac output and electrocardiography	
	Quiz 2	
5	Vasculature	
6	Haemodynamics	

	Quiz 3	
7	Respiratory system	
8	Nervous system	
	Quiz 4	

1.3 Course objectives and learning outcomes

This course introduces the basic concepts and applications of pharmacokinetic modelling, the structure of the cardiovascular system, electrical activity of the heart as well as the structure and function of the respiratory and nervous systems. This course also considers how these processes give rise to changes that can be measured externally from the body.

After attending these lectures, working through the associated example sheet and discussing the material with your tutor, you should:

1. Have a good basic understanding about the anatomy and physiology of the human body.
2. Have knowledge of compartmental models describing compound or drug concentration in the human body.
3. Understand the physiological absorption, distribution, metabolism and elimination of foreign substances in the body and be able to calculate the concentration-time curves of these compounds using pharmacokinetic modelling techniques.
4. Understand the heart and cardiovascular system, the basics of electrocardiography as well as how to read a simple electrocardiogram and to measure blood pressure.

5. Be able to model the vasculature using an electrical equivalent circuit model and to calculate the relevant model parameters.
6. Be able to describe the function of the lung and to calculate lung volumes, respiratory capacity, gas exchange, blood pH and other relevant parameters.
7. Be able to describe the function of the nervous system, including afferent and efferent nerves, and the sympathetic and parasympathetic nerves.

1.4 Recommended books

Physiology for Engineers Michael Chappell and Stephen Payne, 2nd ed., Springer 2020. The book of the course.

Mathematical Physiology (Vols. 1 + 2): J. Keener and J. Sneyd, Springer-Verlag, 2008. A very mathematical treatment of this subject that often goes beyond what we need for this course. Read selectively and stick to the simpler examples.

The following books, in no particular order, might be useful further references:

Cellular Physiology of Nerve and Muscle: G.G. Matthews, 4th ed., Blackwells, 2003. A very good reference although not always quite as mathematical as we want for this course.

Electronic library copy:

<http://oxford.eblib.com/patron/FullRecord.aspx?p=428063>

Molecular Cell Biology: Lodish et al. A classical biology textbook that will help you to put some of the concepts we discuss in the course in a biological context.

Various libraries in Oxford have electronic versions available, check on [Solo](#).

Berne & Levy Physiology: B.M. Koeppen & B.A. Stanton, 6th ed., Mosby/Elsevier, 2010.

The Cardiovascular System at a Glance: P.I. Aaronson and J.P.T. Ward, Blackwells, 2007.

Cardiovascular Physiology: D.E. Mohrman and L.J. Heller, 6th ed., McGraw-Hill, 2006.

These books are all introductory guides to the underlying physiology and are very readable. They do contain a lot of detail and are primarily aimed at medical students, so read selectively. In particular, the sections on the diagnosis of clinical conditions are not relevant.

Two excellent introductory websites are:

http://training.seer.cancer.gov/module_anatomy/anatomy_physiology_home.html

<http://cvphysiology.com/index.html>

For a much more comprehensive overview of the whole subject of Biomedical Engineering refer to:

The Biomedical Engineering Handbook (Vols. 1-3): ed. J.D. Bronzino, 3rd ed., CRC press, 2006.

2 Kinetic modelling

We have already looked at the kinetics of reactions in the first part of this course, here we now consider how kinetic modelling is applied at the system level. We will see that kinetic models and in particular compartmental models appear in various guises. To introduce the topic we are going to look at their use in pharmacokinetics.

2.1 Pharmacokinetics

Pharmacokinetics, often abbreviated to PK, is concerned with the fate of substances introduced into the body; most obviously this includes therapeutic agents, but might also include things like toxins. PK is widely used to study substances in the whole body, for example where a drug has been delivered by injection and subsequently blood samples have been taken to determine the plasma concentration as a function of time. From these measurements we are interested in inferring what happened to the drug: how rapidly it was absorbed into tissues, how quickly it was removed from the body etc. However, PK also applies in various imaging modalities, such as Positron Emission Tomography that you will meet later in the course, where some form of contrast agent is introduced and we want a spatially resolved map of absorption etc. Whilst PK follows what happens to the substance in the body it is also important to know what that substance is doing to the body, which is the aim of pharmacodynamics – something that we will not consider here.

2.2 ADME principles

Pharmacokinetics is commonly divided into a number of separate processes, referred to (for obvious reasons) as the ADME scheme, Figure 2-1:

- **Absorption** is concerned with how the substance taken up into the blood stream or a specific tissue where it has been introduced.
- **Distribution** is concerned with how the substance is distributed throughout the body, most commonly how it goes from blood to tissue and back again.
- **Metabolism** is the conversion of the substance into other products usually via enzyme reactions.
- **Excretion** is the removal of the substance from the body, for example via the kidneys.

The final two processes together represent **elimination**, since they both result in the loss of the substance. In some cases we might also need to be concerned with **liberation**, the release of the substance we are interested in from the formulation that was used to introduce it. Most of these processes, particularly absorption and distribution, will involve some form of transport process to get the substance across membranes in the body. We have already looked at the various passive and active transport processes through which this might be achieved.

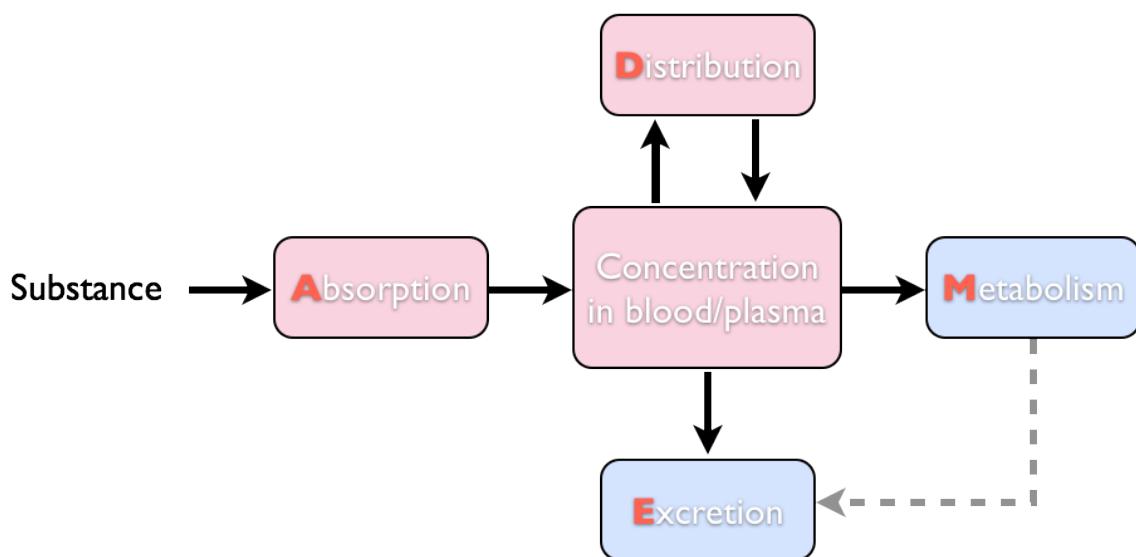


Figure 2-1 ADME principles

2.3 Compartmental models

Whilst there are a number of strategies to do PK modelling we will follow the method of compartmental modelling. In this approach the substance is contained by and moves between different compartments. These compartments are very broadly defined and may not represent any specific part of the body, but rather a collection of tissues that share similar properties. The appeal of this method is that the model remains simple and we have some hope of using it to interpret the data, the disadvantage being that it can be harder to then interpret the model in terms of the underlying physiology.

2.3.1 One compartment model

We will start with the simple model shown in Figure 2-2; in this case we have a single compartment into which the substance is absorbed and out of which it is eliminated. This is most likely to represent a substance in the blood plasma that is unable to cross into the tissues, thus we will talk about the concentration in this compartment as the plasma concentration. If we assume a first order output describes the excretion process with a constant k_e then we can write a differential equation for the system, ignoring the input for the time being, as:

$$\frac{dC_p}{dt} = -k_e C_p(t)$$

If we assume the substance is introduced instantaneously into the system then we can define the input via the initial conditions as the concentration (mass / unit volume) at time 0, i.e. $C_p(0)$. Solving this equation gives a simple exponential decay for the plasma concentration:

$$C_p(t) = C_p(0)e^{-k_e t}$$

(this is the “impulse response” of the system) Thus it would be possible to determine k_e from data of C_p measured through blood sampling. From this we can also define the half-life of the substance as the time taken for 50% of the

substance to be eliminated: $T_{1/2} = \frac{\ln 2}{k_e}$. We might also be interested in the apparent volume of distribution for the compartment, which can be determined simply by dividing the dose given by the initial concentration observed:

$$V_c = \frac{D}{C_p(0)}$$

This is the volume of the compartment into which the substance has distributed itself. This allows us to define the total body clearance, the hypothetical volume of plasma totally cleared of the substance per unit time:

$$Cl_{total} = k_e V_c$$

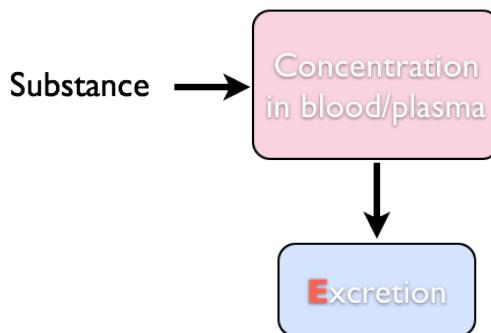


Figure 2-2 One compartment model

In the case of an intravenous injection it will actually take a short time from injection for the drug to have distributed throughout the whole circulation. Additionally, excretion will not begin until the substance has reached the right area of the body. Thus $C_p(0)$ will often be taken shortly after injection once a steady 'initial' condition should have been reached.

We can generalise our model for any arbitrary input as:

$$\frac{dC_p}{dt} = -k_e C_p(t) + C_{in}(t)$$

It is also useful to write the equivalent expression for the total amount of the substance, A_p :

$$A_p = V_c C_p$$

$$\frac{dA_p}{dt} = V_c \frac{dC_p}{dt} = -V_c k_e C_p(t) + A_{in}(t)$$

This allows us to deal with the case of continuous intravascular infusion: setting $A_{in}(t) = k_0$ (a step input at $t = 0$) and solving for C_p gives:

$$C_p(t) = \frac{k_0}{V_c k_e} (1 - e^{-k_e t})$$

From which we can determine the steady state concentration as $t \rightarrow \infty$. Once again we can define $T_{1/2}$, now it tells us how long it takes for 50% of the steady state concentration to be reached, with the steady state being achieved after approximately 5 half lives.

Using Laplace transforms, the impulse response and the property $\mathcal{L}^{-1}\{F(s)G(s)\} = f(t) * g(t)$ we can also derive the more general result:

$$C_p(t) = \frac{1}{V_c} A_{in}(t) * e^{-k_e t}$$

which you should recognise as the convolution of the input function with the impulse response of the system. The impulse response here represents the response following an instantaneous injection $A_{in}(t) = D\delta(t)$, where $\delta(t)$ is the Dirac delta function. This allows us to consider any arbitrary intravenous introductions, such as a series of injections or an infusion with a given duration.

2.3.2 Absorption compartment

So far we have considered only a first-order output. However if the substance is administered orally it has to pass through at least one membrane to get into the plasma. This requires a first order input, as in Figure 2-3. Now we have two equations:

$$\frac{dA_a}{dt} = -k_a A_a(t) + A_{in}(t)$$

$$\frac{dA_p}{dt} = k_a A_a(t) - k_e A_p(t)$$

Note that our convolution result above can be applied here. We could also write the equation for the amount of substance being eliminated:

$$\frac{dA_e}{dt} = k_e A_p(t)$$

from which we could solve for $A_e(t)$. This might be useful if we were able to make some direct measurements of elimination, for example urinary sampling.

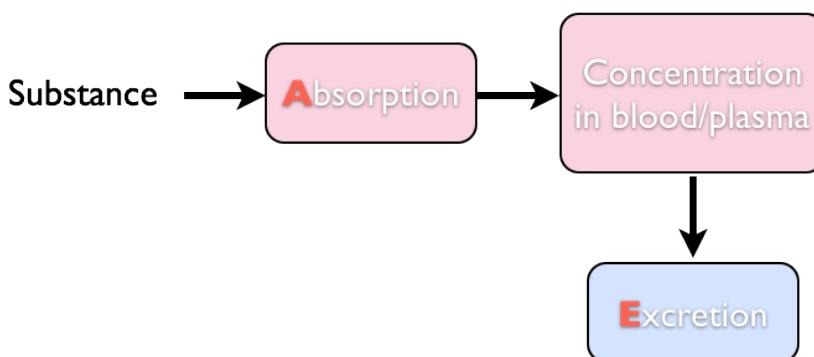


Figure 2-3 One compartment plus absorption model.

For a single oral dose of substance (assume $A_{in}(t) = D\delta(t)$) we can solve to give the plasma concentration as:

$$C_p(t) = \frac{FD}{V_c} \frac{k_a}{k_a - k_e} (e^{-k_e t} - e^{-k_a t})$$

where we have also included, F the bioavailability of the substance. This is the fraction of the delivered dose that actually appears in the blood, taking into account losses in the gut through incomplete absorption and metabolism, as well as excretion in the liver. This can be estimated as the ratio:

$$F = \frac{AUC(C_p(t)_{oral})}{AUC(C_p(t)_{iv})}$$

In words: the area under the plasma concentration-time curve for oral delivery divided by the AUC for the same dose of drug delivered intravenously.

2.3.3 Peripheral compartment

Finally we will consider a substance that also exchanges from the plasma into the tissue – i.e. the distribution process. This requires us to add a further component to the model Figure 2-4. We now have a ‘central’ compartment, which includes plasma, but may also include tissues into which the substance rapidly exchanges (such that we are unable to distinguish them from plasma), and a peripheral compartment. Hence it is generally called a two-compartment model, note that the absorption process is not usually referred to as a compartment even though it behaves as one. The equation for the central compartment is now:

$$\frac{dA_p}{dt} = k_a A_a(t) - k_e A_p(t) - k_{12} A_p(t) + k_{21} A_g(t)$$

where $A_g(t)$ is the amount of substance in the peripheral compartment. The equation for the peripheral compartment is:

$$\frac{dA_g}{dt} = k_{12} A_p(t) - k_{21} A_g(t)$$

This can be solved straightforwardly using Laplace transforms to obtain an impulse response function for the system. With the simple cases of single dose and infusion input that we have considered so far we will then obtain solutions for C_p that are a sum of exponential terms.

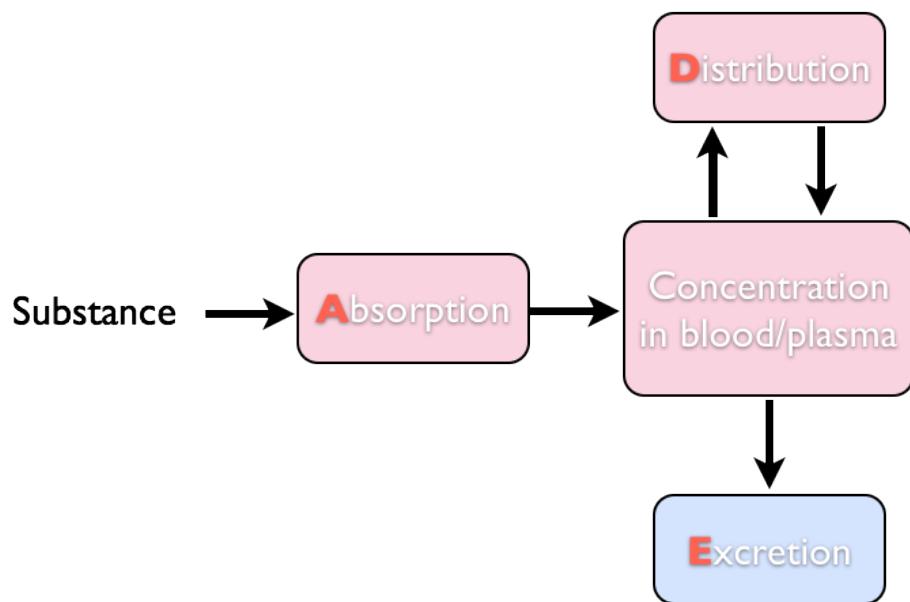


Figure 2-4: Two compartment model (with absorption).

In pharmacological studies we generally have access only to measure concentrations in the plasma compartment and need to try and determine all the unknowns of the system from that. When using contrast agents in imaging, often called **tracer kinetics**, we can measure the substance in the peripheral space too, but we may only be able to measure the sum of plasma and peripheral space concentrations, not the individual quantities.

2.3.4 Multi compartment models

We can build increasingly complex compartmental models if we need to include different peripheral compartments with differing rates of exchange, these will often represent organs (of groups of organs). The model might also need to account for the metabolism of the substance whilst in the tissue into various products (which may or may not then exchange back into the plasma). Metabolism is simply the result of a reaction thus the reaction kinetics we saw at the start of the course can be applied and at their simplest match those we have been using here, which should not be a surprise since both are called kinetics. If the metabolic products do end up in the blood stream it might be possible to sample them too and thus quantify more about the system.

Spectroscopic imaging systems also permit the measurement not only of the substance that has been introduced but also some of the products it converts into.

A way to get around (or summarise) the complexity of a multi compartmental model is to return to the convolution expression we had earlier, but now write the plasma concentration as:

$$C_p(t) = C_{in}(t) * R(t)$$

where $R(t)$ is the impulse response of the system (and gives rise to a transfer function in the Laplace or frequency domain). This impulse response function can be interpreted as the fraction of the substance that arrived at any point in time that is still present at some time later. (If that seems a bit puzzling it is worth revising how the convolution operation works). In some cases, particularly tracer kinetics, we might know (or be able to guess at) the input function and thus can try and estimate the impulse response function directly, normally via some form of numerical deconvolution.

2.3.5 Non-linear models

So far all of the compartmental models have been linear. However, we have already met various non-linear processes in reactions and transport. Hence, more physiologically accurate models might incorporate some non-linear terms. The most common way to model non-linearities is to use Michaelis-Menten kinetics (see lectures 1-4):

$$\frac{dC_p}{dt} = \frac{V_{max}C_p}{C_p + K_m}$$

where K_m is the Michaelis constant. This can be regarded as approximately first order if $C_p \ll K_m$ or zero order (saturated) if $C_p \gg K_m$

3 Cardiovascular system I: The heart

The final three lectures each address a system in the body. Here 'system' refers to a collection of organs that can be grouped together to perform a function or range of related functions.

The focus here will be on three of the most medically significant systems, namely the cardiovascular, respiratory and nervous systems. You will look at some of the other systems elsewhere in the course. We will consider both how we can give a quantitative description of the physiology of these systems as well as start to look at how we might make quantitative measurements, a topic that you will come back to in other parts of the course.

3.1 Overview of the cardiovascular system

The cardiovascular system, which is alternatively known as the circulatory system, comprises the human heart, blood vessels and blood. It has five main functions:

- Distribution of O₂ and nutrients, for example glucose and amino acids, to all body tissues.
- Transport of CO₂ and metabolic waste products from the tissues to the lungs and other excretory organs.
- Distribution of water, electrolytes and hormones throughout the body.
- Contributing to the infrastructure of the immune system.
- Thermoregulation.

Its overall aim is to maintain the body within well-defined limits, irrespective of external stimuli: this equilibrium is termed *homeostasis*.

A schematic outline of the system is shown in Figure 3-1 with the heart at the middle: the blood flows in a continuous loop, from the right ventricle to the lungs (where carbon dioxide in the blood is removed and exchanged for oxygen), to the left atrium and left ventricle, out to the body tissues (where oxygen passes into the tissue in exchange for carbon dioxide) and back into the right atrium and ventricle. Note that, although the lungs are a single entity, the remainder of the body tissue is spread out over the entire body. The main body tissues in descending order of blood flow rate are the kidney, spleen, skeletal muscle, brain, skin, liver, bone, and heart muscle. The circulation is sometimes divided into pulmonary and systemic components. The pulmonary circulation comprises the lungs and the systemic circulation all the body tissues.

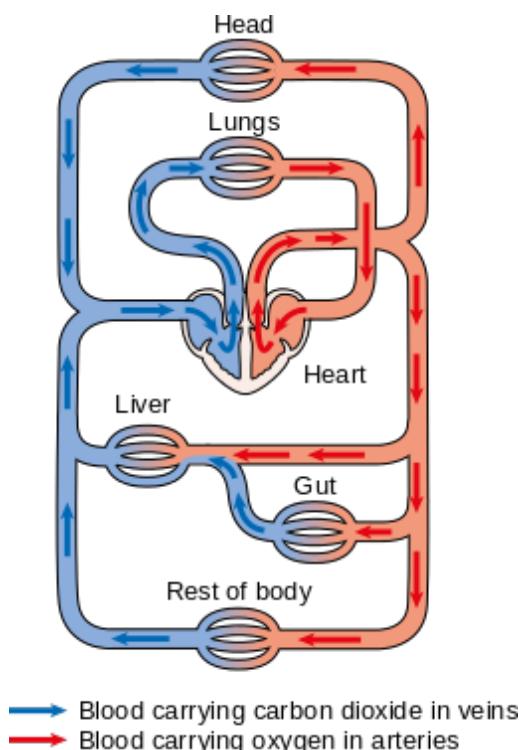


Figure 3-1 Schematic of cardiovascular system

By Cancer Research UK under [CC-BY-SA-4.0](#), via Wikimedia Commons

3.2 Structure and operation of the heart

The most important part of the system is the heart, which acts as the pump driving blood round the body. A healthy adult heart pumps approximately 5 litres

of blood around the body every minute. Over the course of a 70-year life span, a heart will beat several billion times and deliver over 100 million litres of blood.

A schematic of the structure of the heart is shown in Figure 5.2. The main division is into the left and right sides (NB this is a frontal view, and the directions left and right refer to the human whose heart this is). The left side pumps oxygenated blood from the lungs to the tissues, whilst the right side pumps de-oxygenated blood from the tissues back to the lungs. The sides are often coloured red and blue respectively to denote these functions. Although oxygenated blood is bright red, de-oxygenated is not blue but a darker red.

Both sides are subdivided into an atrium and a ventricle: there are thus four chambers. The two atria are thin-walled and receive blood from blood vessels called veins (pulmonary veins on the left side and superior and inferior vena cava on the right side), whereas the two ventricles are thick-walled and pump blood out into vessels called arteries (the aorta on the left side and the pulmonary arteries on the right side). Note how the aorta forms an arch, turning the main blood flow stream through 180 degrees – the main flow is directed upwards out of the left ventricle and is then turned downwards into the abdomen.

There are two types of valves: outflow valves, and atrioventricular (AV) valves. Outflow valves are also called semilunar valves because they are made up of three crescent-shaped flaps called cusps. These valves, the pulmonary valve and the aortic valve, open to allow blood to flow out into the pulmonary artery or aorta, respectively, when the ventricles contract and close to prevent backflow between contractions.

The atrioventricular (AV) valves separate the atria from the ventricles. They open when the atria pump blood into the ventricles, and they close when the ventricles contract to prevent backflow into the atria.

The cusps of these valves are usually called leaflets. They are attached by strings called chordae tendonae to papillary muscles on the inside of the ventricle walls. The right AV valve has three leaflets and is therefore called the tricuspid valve. The left AV valve, with two leaflets is most commonly called the mitral valve.

The heart wall is comprised of three layers: the epicardium, myocardium and endocardium, from outer to inner. The endocardium is a thin layer of cells, similar to the endothelium of blood vessels; the myocardium is the muscle and the epicardium is the outer layer of cells. The whole heart is contained within the pericardium, a thin fibrous sheath or sac, which prevents excessive enlargement. The pericardial space contains interstitial fluid as a lubricant.

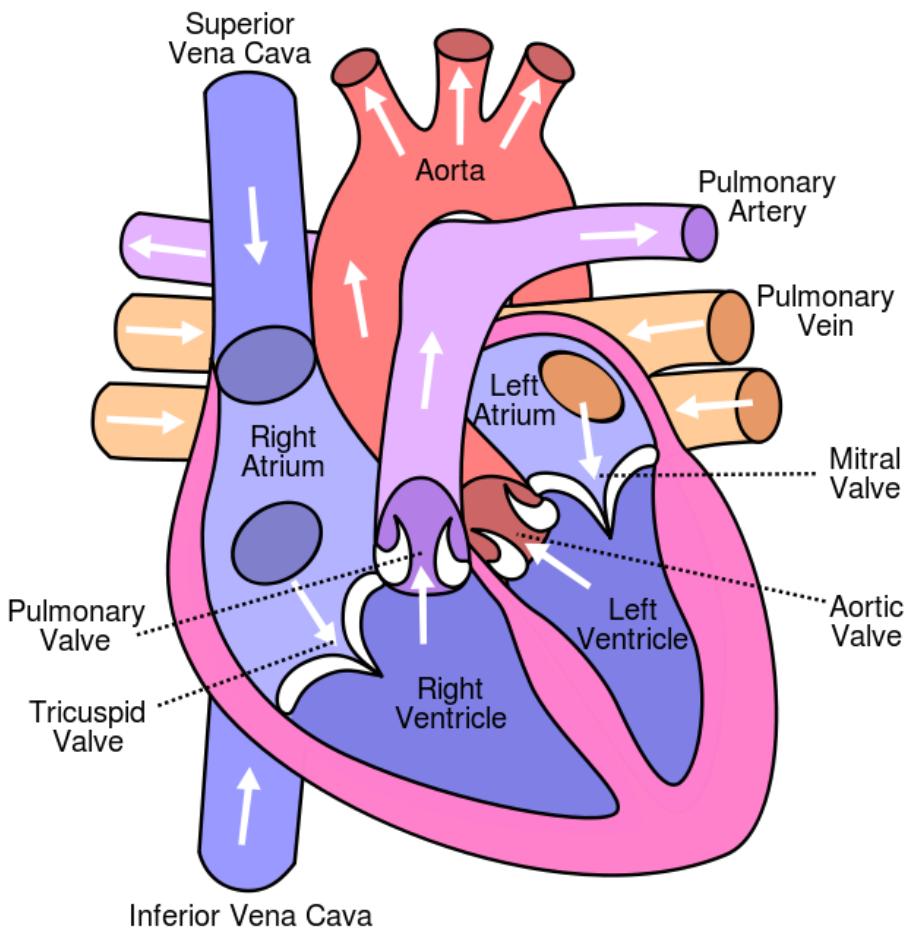


Figure 3-2: Schematic of heart

Blausen 0168 CardiovascularSystem by Blausen Medical Communications, Inc. Licensed under Creative Commons Attribution 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Blausen_0168_CardiovascularSystem.png

The cardiac cycle comprises two parts: the resting (or filling) phase, termed **diastole** (“expand”), and the contractile (or pumping) phase, termed **systole** (“Squeeze”). During diastole, blood enters the heart on both sides simultaneously through the veins. The pulmonary and aortic valves are both shut, so the atria and ventricles expand. During systole, the heart contracts strongly and the pulmonary and aortic valves open: a pulse of blood thus flows out into the pulmonary arteries and aorta. However, it is important to remember that blood is still flowing in through the veins: the heart must still accept this blood and ensure that blood is not forced back into the veins.

This is when the separate chambers become important: the tricuspid and mitral valves are shut automatically by the pressure that builds up in the ventricles and so the atria continue to receive blood whilst it is being forced out of the ventricles. The structure of the tricuspid and mitral valves is the reason for this unidirectional behaviour, since they are attached to the ventricular walls and thus permit flow through in one direction only. Similarly, when the ventricles relax, the pulmonary and aortic valves act to prevent blood from flowing back into the ventricles: these valves are thus also unidirectional.

Note that the heart valves behave in a very similar way to electrical diodes, where the current can only flow one way. In fact there is always some leakage in the heart valve, just as there is in the diode, but in a healthy individual the level is such that it can safely be ignored. The structure of the heart thus enables it to receive a constant flow of blood through the veins, whilst pumping out blood at regular intervals through the arteries. It is important to remember that the body thus receives a pulsatile, rather than a steady, flow of blood.

The myocardium is the muscle in the heart wall whereby the heart contracts and obviously it must be supplied with blood to function properly. The cardiac muscle thus has a network of blood vessels to supply it, via the left and right coronary arteries, which branch off the ascending aorta. After passing through the myocardium these vessels feed back to the right atrium via the coronary sinus. The operation of the coronary system is thus vital: hence the need for coronary bypasses if the vessels become blocked.

Ischemic heart disease is caused by an imbalance between the blood flow to the myocardium and the myocardial metabolic demand. Atherosclerosis, also known as hardening of the arteries, is a build-up of fatty plaque on the inside wall, increasing the resistance to flow, and reducing the supply of blood. A myocardial infarction (the proper term for a heart attack) means that some of the heart muscle cells die due to this lack of supply. This death can cause irregular rhythms, which can be fatal even if there is enough healthy muscle to continue pumping. After myocardial infarction, the heart can recover, even though it will not be able to pump as much as before. Nowadays, most patients survive heart attacks and can live long and healthy lives afterwards. The heart thus plays a crucial role in the operation of the human body: if it stops operating for even a few minutes, the build-up of waste products and starvation of nutrients leads rapidly to irreversible cell death.

3.3 Measurement of cardiac output

Given the importance of the heart in the operation of the human body, it is obviously important that we monitor its behaviour. One of the measures of the heart's performance is termed Cardiac Output (CO): this is the rate at which the heart pumps blood out into the pulmonary and systemic circulation. There are a variety of ways to measure CO, both directly and indirectly.

The first technique is based on Fick's principle, which equates the absorption of oxygen in the capillaries to the oxygen inhaled in the lungs (balancing the input and output of oxygen in the body). The absorption of oxygen in the capillaries can be calculated as the difference between the oxygen contents in the arteries $O_2_{arterial}$, and the veins, O_2_{venous} : these are normally measured in units of $\text{ml}_{O_2} / \text{ml}_{\text{blood}}$. The oxygen consumption of the body V_{O_2} , measured in

ml_{O_2} / minute, is then the product of this difference and the CO, measured in ml_{blood} / minute. CO can thus be calculated by:

$$\text{CO} = \frac{V_{\text{O}_2}}{(O_{2\text{arterial}} - O_{2\text{venous}})}$$

A second technique uses indicator dilution. If a known amount of a substance is injected into an unknown volume, the final concentration allows the volume to be calculated. In Hamilton's dye method a quantity of non-toxic dye is injected into a vein: it mixes with the blood as it passes through the heart and lungs. By taking successive arterial blood samples, the mean concentration can be calculated. Cardiac output is estimated from:

$$\text{CO}_{\text{dilution}} = \frac{A_p^{\text{dye}}}{C_p^{\text{dye}} \cdot t_{1\text{pass}}}$$

i.e. the ratio of the Amount of Dye Injected A_p^{dye} to the product of the Mean Dye Concentration $\overline{C_p^{\text{dye}}}$ with Duration of First Passage $t_{1\text{pass}}$. This product is itself an estimate of the area under the C_p^{dye} pharmacokinetic curve for one passage of the dye.

A variant on this is the thermodilution technique, which is the most common method to measure CO. A modified Swan-Ganz catheter with a thermistor at its tip and an opening a few centimetres from the tip is inserted from a peripheral vein such that the tip is in the pulmonary artery and the opening is in the right atrium. A small amount of cold saline is injected into the atrium and this mixes with the blood as it passes through the ventricle and into the pulmonary artery, thus cooling the blood. By measuring the blood temperature, the flow rate can

be calculated, since the temperature drop is inversely proportional to the blood flow. This is very similar to the indicator dilution technique, but measuring the dilution of temperature rather than concentration.

A modern non-invasive technique (i.e. a technique that does not require the insertion of any probes into the body) is to use imaging methods to estimate real-time changes in the size of the ventricles. This gives the Stroke Volume (SV): the volume of blood pumped out in one cardiac cycle. The CO can then be calculated from:

$$CO = SV \cdot HR$$

3.4 Electrical activity of the heart

Thus far, we have simply considered the mechanical activity of the heart, by considering the heart as a pump and thinking in terms of blood flow. We will now turn our attention to the electrical activity of the heart, by considering what drives it, in particular what makes it expand and contract, before considering how we can monitor its performance. This builds upon the earlier lectures on the derivation of the action potential.

3.4.1 The action potential

The action potential of a cardiac muscle cell, Figure 3-3, is similar to that of the cells that we examined in lecture 3, with the addition of a sustained plateau due to the influence of Ca^{2+} .

Depolarization: This is the first phase of cardiac cell firing (known as phase 0): this phase lasts approximately 2 ms. Like the skeletal muscle cell example we followed previously the action potential is generated by a sudden transient rise

in Na^+ permeability with a subsequent increase in potassium permeability (remember the m , n and h gates). The inward current of Na^+ ions through voltage-gated Na^+ channels becomes sufficiently large to overcome the outward current through K^+ channels and so the cell potential increases (becomes less negative): the membrane thus becomes much more permeable to Na^+ ions due to the channels. This process then activates more Na^+ channels and the process becomes self-perpetuating (essentially unstable).

Plateau: When the membrane potential reaches a threshold, voltage-dependent calcium channels open and there is a large influx of calcium ions. There are also some potassium channels that close during this phase (the opposite to the potassium channels discussed in lecture 3). These two effects contribute to the plateau, where the membrane potential decays slowly over approximately 250 ms (phase 2), even though the sodium permeability returns virtually to its resting value.

Repolarization: The next stage is a more rapid drop (phase 3). This is due to a gradual decline in the calcium permeability and an increase in potassium permeability. The precise mechanisms are still not fully understood, but the decline in $p\text{Ca}^{2+}$ may be due to the effect on the Ca^{2+} channels of accumulation of Ca^{2+} in the cells. By the end of phase 3, the outward K^+ current returns to its dominant position and the membrane potential returns to its resting value before the next action potential begins.

Since the action potential automatically causes a mechanical response, with the tissue contracting and becoming shorter in length in response, it might be

wondered why there is a need for a more complicated action potential. This is because in cardiac muscle, the duration and strength of the contraction are important parameters that will have to be adjusted dependent upon the circumstances: more control is needed over the action potential and this is achieved through the calcium level changes.

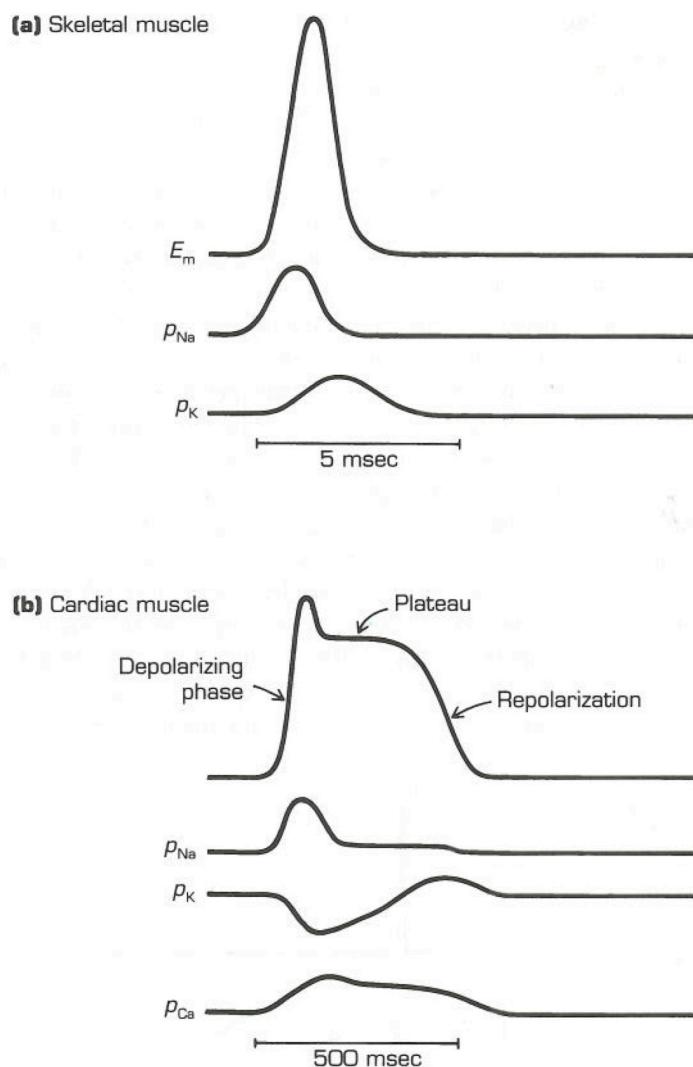


Figure 3-3 Skeletal and cardiac muscle cell action potentials and intracellular ionic concentrations. Matthews p197

3.4.2 Pacemaker potential

Heart cells in isolation beat rhythmically, they exhibit a spontaneous action potential that does not require an external stimulus to start the process, thus they do not exhibit a true resting potential. Like the skeletal muscle example the

cardiac AP has a phase where the open K⁺ channels slowly close, this was the 'undershoot' for the muscle AP. As the system returns to 'baseline' the threshold is once again reached for depolarization and the whole process restarts. This is referred to as the pacemaker potential. In reality the rate of APs in cardiac muscle cells varies from cell to cell and thus there needs to be some form of co-ordination to ensure that the whole muscle contracts simultaneously.

3.4.3 Cardiac cycle

The stimulus for the cardiac AP is provided by the SinoAtrial Node (SAN), (Figure 6-4). The cells found in the SAN are often termed pacemaker cells. The SAN has an unstable resting potential, which decays from approximately -60 mV to a threshold value of -40 mV, at which an AP is initiated. The rate of decay of this resting potential thus determines the rate of firing and hence the heart rate. In a healthy human at rest, this will result in APs being started approximately 70 to 80 times each minute. As the SAN cells depolarise, they stimulate the adjacent atrial cells, causing them to depolarise similarly. The depolarisation wave spreads over the atria in an outward-travelling wave from the point of origin. Both atria contract nearly simultaneously, as do both ventricles afterwards. Co-ordination between atria and ventricles is achieved by specialised cardiac muscle cells that make up the conduction system, Figure 6-4.

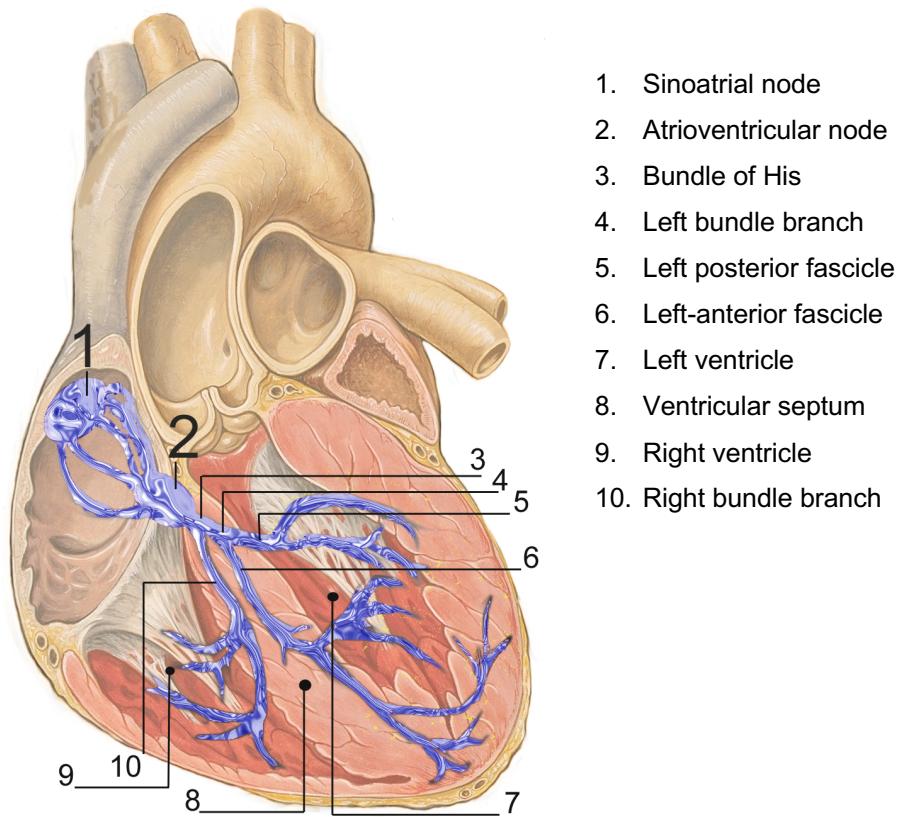


Figure 3-4: Conduction system for the heart

By J. Heuser under [CC-BY-2.5](#), via Wikimedia Commons

The wave is prevented from spreading past the limits of the atria by a fibrous barrier of non-exitable cells: the only excitable tissue that crosses this barrier is the Bundle of His. At the origin of this bundle is a mass of specialised tissue about 2 cm long and 1 cm wide called the AtrioVentricular Node (AVN). The conduction velocity through the AVN is approximately 0.1 m/s, some 10 % of that of the atrial cells. The delay that this causes is vital in preventing the ventricles from contracting before the atria have completed their contraction. The impulse from the AVN travels through the Bundle of His, which splits into the left and right bundle branches before dividing into the multiple fibres of the Purkinje system. This distributes the impulse over the inner walls of the ventricles causing contraction.

Although the SA node alone would produce a constant rhythmic heart rate, there are regulating factors present, as the heart rate may need to increase, for example for increased physical activity, or decrease, for example when sleeping. This is largely controlled by the AVN. Most of the changes in the heart rate are mediated through the cardiac centre in the brain via the sympathetic and parasympathetic nervous systems. There are a large number of factors involved that affect the heart rate, such as body temperature, ion concentrations, oxygenation levels, blood pressure and even emotions.

The heart rate increases to increase Cardiac Output (CO). There are three factors to consider that can affect CO: the filling pressure of the right heart (the preload), the resistance to outflow from the left ventricle (the afterload) and the functional state of the heart. The last includes heart rate and contractility: the ability of cardiac muscle to generate force for any given fibre length.

The Stroke Volume (SV) depends on the ventricular end-diastole volume (EDV), according to the Frank-Starling law of the heart, such that an increase in this volume causes an increase in SV. The maximal pressure that can be developed by the ventricle at any given left ventricular volume is defined by the end-systolic pressure-volume relationship (ESPVR). Figure 3-5 shows the pressure-volume relationship for the left ventricle: increases in preload increase the SV, but increases in afterload decrease SV, as the loop moves upwards and the left side to the right. Increases in contractility move the ESPVR line upwards, thus increasing SV.

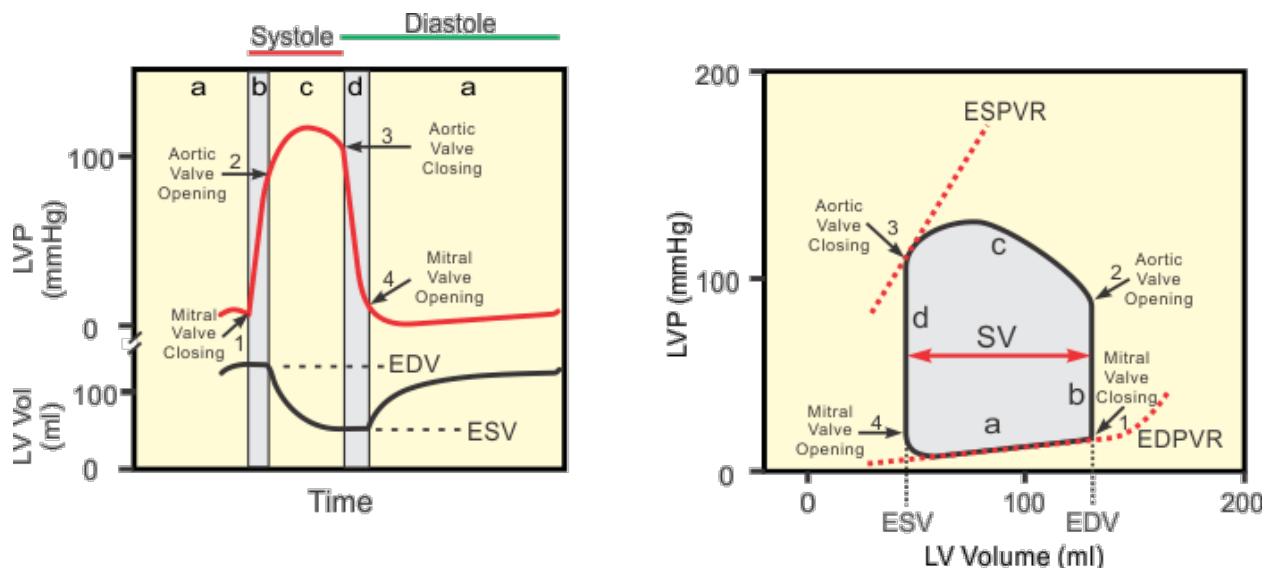


Figure 3-5: Variation in left ventricle pressure and volume over cardiac cycle

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3.5 Introduction to electrocardiography

The pumping cycle is controlled by a conduction system to give a series of events in a very well-defined order. The conduction system generates current densities by the membrane activity of the heart muscle cells. These ionic currents flow in the thorax, which contains no other sources or sinks and is thus a purely passive medium. Currents flowing through resistive loads produce voltages (they are of course very small): by placing electrodes at different positions on the human body, the potential differences can be recorded. These potentials form the basis of the ElectroCardioGram (ECG). The difficulties encountered in attempting to measure very small potential differences (of the order of a few mV) on a living human will be examined in the Medical Electronics lectures. We will confine ourselves to understanding the production of the signal.

The ECG is based on the idea of an equilateral triangle (known as Einthoven's triangle) with the heart as a current source at the centre, Figure 3-6. Since the potential difference depends upon both the current magnitude and direction, the

ECG is a vector quantity. In conventional ECG the three bipolar leads, i.e. measurements made between two points, are known as Lead I (right arm to left arm), Lead II (right arm to left leg) and Lead III (left arm to left leg). There are then a further nine unipolar leads, i.e. measurements made at one point): aVR (right arm), aVL (left arm), aVF (left leg) and V₁ to V₆, Figure 3-6.

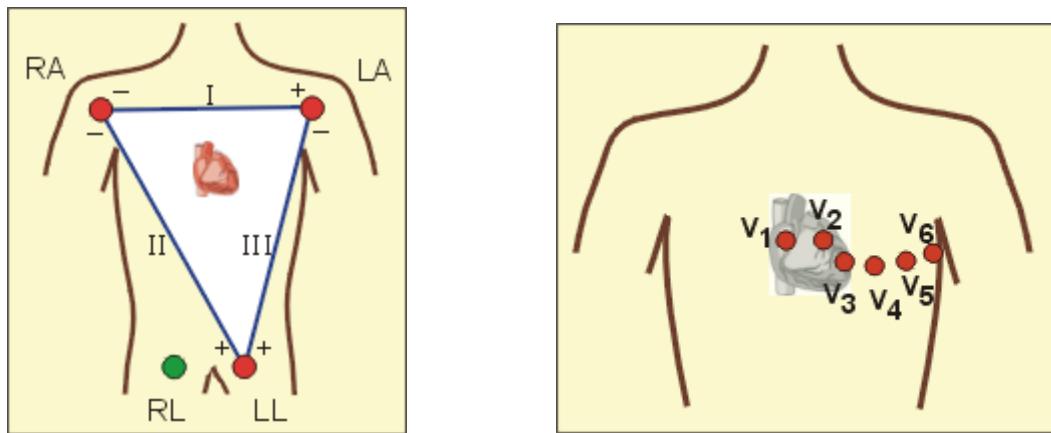


Figure 3-6 Electrode labels

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Although each of these 12 leads will give a different output, the characteristics of the heart cycle are most clearly shown in lead II, which is the most commonly used. A typical waveform is shown in Figure 3-7. It is labelled at various points: P, Q, R, S and T.

- P wave: The depolarisation of the atria prior to atrial contraction causes a small low-voltage deflection, followed by a delay.
- QRS complex: The depolarisation of the ventricles prior to ventricular contraction causes a large voltage deflection: this is the largest-amplitude section of the ECG. Although atrial repolarization occurs before ventricular depolarisation, the resulting signal is very small and thus not seen.
- T wave: Ventricular repolarization. This last section is much the most variable and often very hard to see.

The sections between these features are close to zero potential.

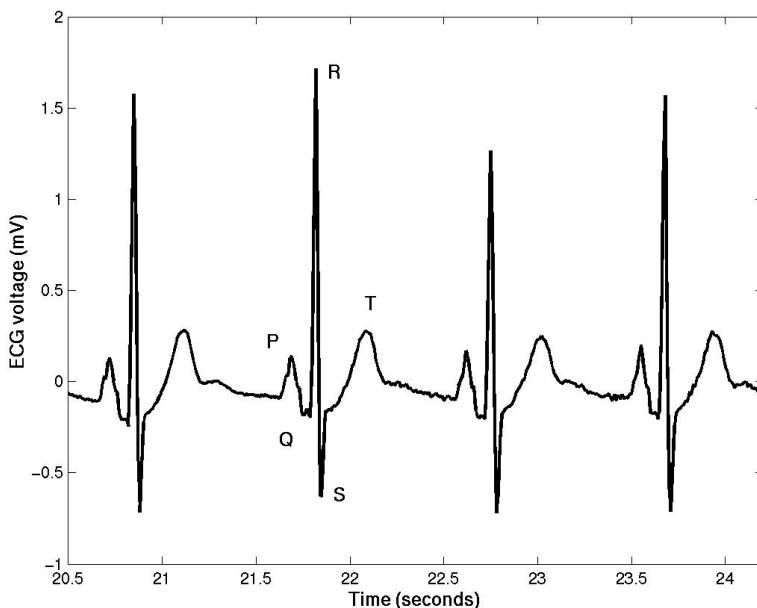


Figure 3-7 Typical ECG

Although the ECG only provides information about the timing of the heart's operation, rather than its output, a huge amount of research has been done to interpret the ECG in terms of providing clinical diagnoses. The simplest measure that can be extracted is the heart rate, normally taken as the inverse of the time between successive R peaks (the RR interval), measured in beats per minute. A trained clinician will also be able to infer much more information about the state of the heart from an ECG, using changes in the relative timings and amplitudes of different sections of the ECG. Measurement of the ECG is also simple and cheap, meaning that it is normally the first monitoring device used on a patient.

A summary of the cardiac cycle is shown in Figure 3-8, relating the ECG to the pressure and volume changes in the left ventricle. Systole comprises phases 2-4 inclusive, whilst diastole comprises phases 5-1 inclusive. At the beginning of stage 2 there is ventricular depolarisation (QRS complex), which causes the pressure

in the left ventricle to increase rapidly and the volume to drop. When the pressure reaches the aortic pressure the aortic valve opens and blood leaves the ventricle: the pressure thus drops and when it drops below aortic pressure the aortic valve closes again. Ventricular repolarization occurs in stage 4 (T wave) and the ventricles slowly return to their steady state conditions.

Note that there are characteristic heart sounds: S1 to S4. The first heart sound is low frequency and associated with closure of the atrioventricular valves; the second is higher frequency, reflecting a longer ejection period in the right ventricle; the third is associated with rapid refilling and the fourth with atrial systole. Normally only S1-S3 are heard. In Figure 3-8 they appear from left to right as S4, S1, S2, S3.

- Phase 1 Atrial contraction
- Phase 2 Isovolumetric contraction
- Phase 3 Rapid ejection
- Phase 4 Reduced ejection
- Phase 5 Isovolumetric relaxation
- Phase 6 Rapid ventricular filling
- Phase 7 Reduced ventricular filling

Abbreviations:

LV Press, left ventricular pressure

a, a-wave; c, c-wave; v, v-wave

LVEDV, left ventricular end-diastolic volume

LVESV, left ventricular end-systolic volume

LV Vol, left ventricular volume

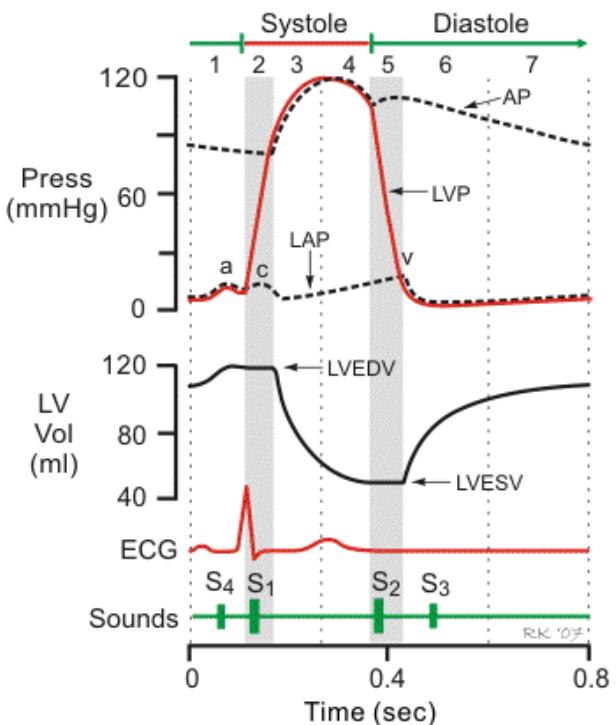


Figure 3-8 Cardiac cycle

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4 Cardiovascular system II: the vasculature

4.1 Anatomy of the vascular system

The blood vessels divide into five main types: arteries, arterioles, capillaries, venules and veins. These types occur in that order and are distinguished by differences in sizes, characteristics and function. The blood exits the heart through the aorta, which then divides into a number of arteries. These divide in turn into arterioles then capillaries before joining together in venules before entering the heart from the veins via the venae cavae. A schematic is shown in Figure 4-1. The vessels shown in bright red are oxygenated, whereas the vessels shown in dark red are de-oxygenated, since the oxygen carried by the blood has been transferred to the surrounding tissues in the capillaries, as described below.

The arteries are thick-walled vessels that expand to accept and temporarily store some of the blood ejected by the heart during systole and then to pass it downstream by passive recoil during diastole. As the arteries branch off, their diameter decreases, but in such a manner that the total cross-sectional area increases several-fold. The arteries have a relatively low and constant resistance to the flow.

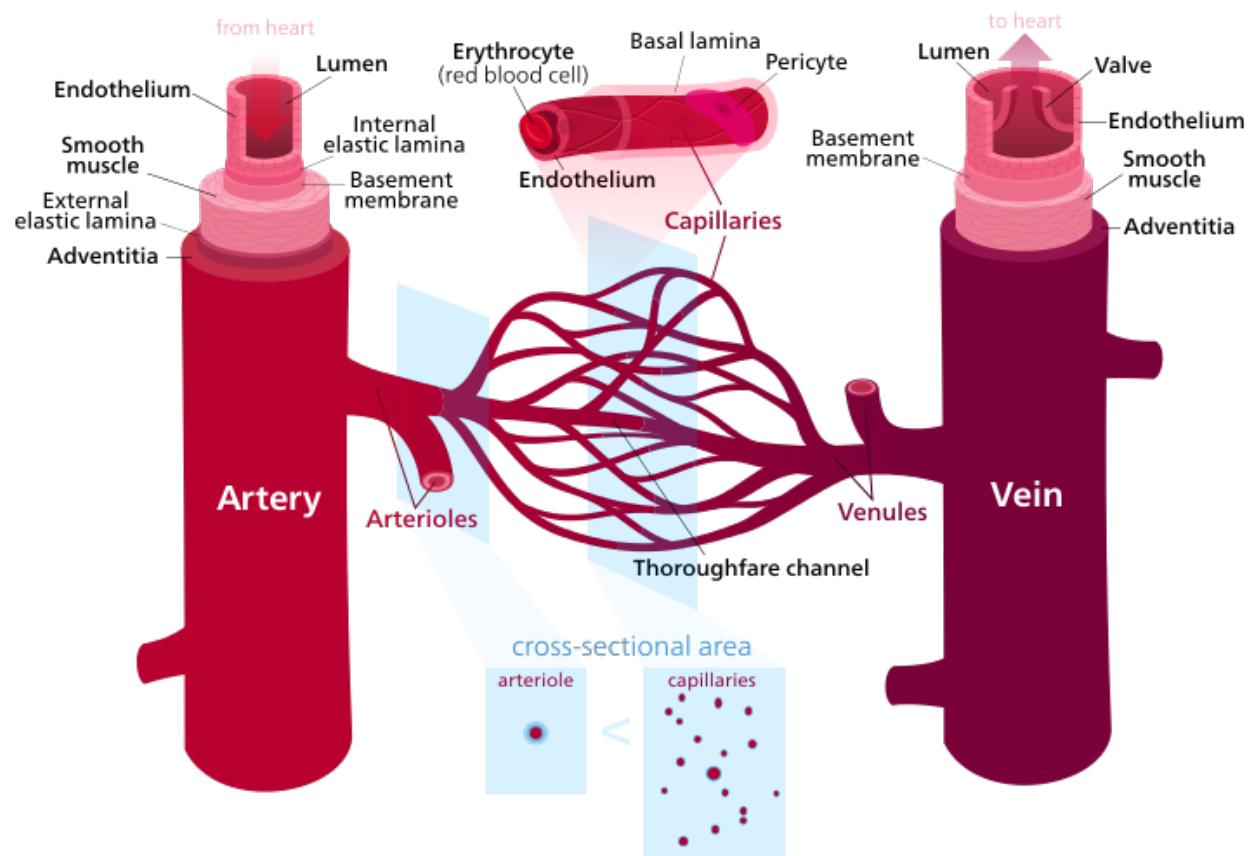


Figure 4-1 Schematic of blood vessels

"Blood vessels" by Kelvinsong. Licensed under Creative Commons Attribution-Share Alike 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Blood_vessels.svg

The artery walls comprise three layers: the tunica intima (or tunica interna), the tunica media and the tunica adventitia (or tunica externa), which are, as their names imply the inner, middle and outer layers. The layers consist of helically arranged collagen and elastin fibres, commonly called "elastic" tissue, providing high extensibility and resilience. The middle layer is mainly smooth muscle and is usually the thickest layer: it is important as it both supports the vessel and changes diameter to regulate the blood flow and blood pressure. A schematic of the artery and vein wall structures is shown in Figure 4-1.

The arterioles have much thicker walls in proportion to their size than the arteries and have a much greater flexibility to change their diameter and hence their

resistance to flow, due to the presence of more smooth muscle. The total flow cross-sectional area is much larger than for the arteries. However, arterioles have a high and changeable resistance, which allows for regulation of the flow to be achieved.

The capillaries are the smallest vessels with very thin walls that contain no smooth muscle: their resistance is thus largely unchanging. The total cross-sectional area is at its largest: therefore the flow velocity is small and this is thus where most of the exchange processes occur. The density and distribution of the capillaries depends upon the requirements of the local body tissues: where the tissues consume high levels of oxygen, there will be a greater density of capillaries. The tissue oxygen consumption level is termed the metabolic rate: tissues such as the skeletal muscle, liver and kidney have a high metabolic rate and thus an extensive network of capillaries.

A reverse branching process occurs as the flow enters the venules and the veins: the vessels branch back together again and the flow velocity increases as the cross-sectional area decreases. The venous vessels have very thin walls in proportion to their diameters: they are thus very distensible and increase in volume significantly as the pressure changes (unlike the arterial and capillary vessels). They normally contain approximately 70 % of the total blood volume at any one time. Just as the arterioles are used to control the resistance, so the venous vessels are used to control the blood volume. There are valves in medium and large veins to prevent blood from flowing backwards, since the veins are mostly travelling up towards the heart and there is very little pressure to force the blood forwards. Venous return primarily depends upon skeletal muscle action

(e.g. calf muscles in your legs), respiratory movements and the constriction of smooth muscle in the venous walls.

Table 4.1 summarises the structural properties of the different parts of the vascular system in more detail: we will consider how these affect the behaviour of the cardiovascular system once we have considered the mechanics of the blood flow through vessels. Note that the number of branches is very large, as the cardiovascular network must cover the entire body.

Table 4.1: Structural properties of the peripheral vascular system (adapted from Bronzino)

	Arteries (Aorta)	Arterioles	Capillaries	Venules	Veins (Vena cavae)
Internal diameter	4 mm (25 mm)	40 µm	7 µm	40 µm	7 mm (30 mm)
Wall thickness	1 mm (2 mm)	20 µm	1 µm	7 µm	0.5 mm (1.5 mm)
Length	20 mm (0.4 m)	2 mm	0.5 mm	0.5 mm	25 mm (0.3 m)
Number	280 (1)	20,000,000	16,000,000,000	160,000,000	260 (1)

4.2 Blood

Blood consists of two elements: plasma and blood cells. Approximately 40-45 % of the volume of blood is occupied by blood cells that are suspended in the watery fluid, plasma. The fraction of blood volume occupied by cells is called the

haematocrit. The plasma consists of ions in solution and a wide range of plasma proteins. By weight it comprises about 90 % water, 7 % plasma protein, with the remainder made up of other organic and inorganic substances. Plasma is the means by which nutrients and waste products are transported. The blood cells are divided into erythrocytes (red blood cells), leucocytes (white blood cells) and platelets. Although they are all produced in the red bone marrow, they have different functions and the white blood cells come in a large number of types.

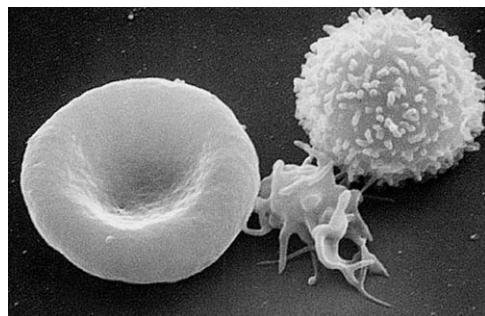


Figure 4-2 Blood cells. From left to right: red blood cell, platelet, white blood cell.

"Red White Blood cells" by the Electron Microscopy Facility at The National Cancer Institute at Frederick (NCI-Frederick). Public domain via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Red_White_Blood_cells.jpg

The red blood cells are by far the most numerous (approximately 5 million per square mm of blood) and they contain the haemoglobin that is responsible for the transport of oxygen. They are biconcave discs and deform easily to pass through the capillaries, since they are approximately 7 μm in diameter, Figure 4-2. The white blood cells defend the body against infection whilst the platelets play an important role in haemostasis (the formation of blood clots in response to damage to the vessel wall). A typical human contains approximately 5.5 litres of blood.

4.3 Haemodynamics

Haemodynamics is the study of the flow of blood. Since blood is a fluid, it can be treated like any other fluid. We will start by assuming that the fluid is Newtonian, that the flow is laminar and steady and that the vessel in which it is flowing is straight and rigid. Although this might seem an enormous set of assumptions to make, it actually gives us a very important result.

The second example sheet asks you to derive the following relationship between the pressure difference along a blood vessel and the flow rate through it:

$$\frac{\Delta p}{q} = \frac{8\mu L}{\pi a^4}$$

where the viscosity of blood is μ and the vessel radius and length are a and L respectively. This is a result for any fluid and turns out to be surprisingly useful. The right-hand side of this equation is effectively the resistance to flow, which can be thought of as analogous to electrical resistance.

An important concept in haemodynamics is the *equivalent circuit*. This works on the basis that the equations for blood flow are very similar to those for charge flow. The basic equation for current and voltage is Ohm's law:

$$\frac{V}{I} = R$$

which is very similar to the previous, where voltage (or potential difference) equates to pressure difference, current relates to blood flow and the ratio of the two is resistance (electrical resistance here and hydraulic resistance in the previous). There is a close relationship between the two equations and this is why the analogy is used so frequently.

Hydraulic resistances can be put in series and in parallel in exactly the same way as electrical resistances. The arteries, arterioles, capillaries, venules and veins flowing to each body organ are thus in series, since blood flows through them consecutively, whereas the body organs are predominantly in parallel, since blood flows through them simultaneously.

The second example sheet asks you to calculate the resistances of all the different parts of the vascular network using Table 4.1. You will find that the resistance is dominated by the arterioles: this is why they are predominantly used to adjust the overall vascular resistance. As their resistance drops, the flow rate will increase for fixed blood pressure or the blood pressure will drop for fixed blood flow. They do, of course, only adjust the resistance within certain limits. The blood flow through each body organ can also be altered by adjusting the relevant arteriolar resistance: since the organs are in parallel, the blood flow can be changed for one organ without having a significant effect on the remainder of the vascular system.

Of course, we have made a large number of assumptions to derive these results. The most important are that the flow is not steady (remember that the heart is a pulsatile pump) and that the vessel radius is not constant. The effects of pulsatile flow and wall diameter are often introduced by means of extra electrical components. Inductance is used to model the inertia of the column of fluid whereas capacitance is used to model the storage of blood in vessels, due to the elasticity of the vessel walls. This storage is a very important feature of the vascular system: in fact, the arteries and veins behave more like balloons with a single pressure, rather than resistive pipes with a continuous decrease in pressure.

The inductance of a blood vessel is found from solving the Navier-Stokes equations under certain conditions (beyond the scope of this course) and is given by:

$$I = \frac{\rho L}{\pi a^2}$$

where ρ is the density of blood. Note that we generally use I for inductance, rather than L , for obvious reasons. The capacitance is calculated from the relationship between flow rate and volume change, which can be compared to the standard form of a capacitor:

$$q = \frac{dV}{dt} = C \frac{d(p - p_{ext})}{dt}$$

where the pressure inside the vessel is calculated relative to the external pressure. Thus:

$$C = \frac{dV}{d(p - p_{ext})}$$

The capacitance thus depends upon the properties of the vessel wall: the interaction between the fluid flow and the vessel wall is what makes haemodynamics such a complex subject.

The artery walls are composites of fibrils of proteins (collagen and elastin) in helical arrangements (Figure 4-2a) that achieve some remarkable mechanical properties. The most important is to sustain a 1 Hz pulsatile strain with magnitude of approximately 10% (in the aorta) for around 70 years without failure. Another is to enable large radial expansion of the artery without significant axial lengthening. In confined spaces in the body, and especially for arteries supplying the brain inside the skull, lengthening would lead to buckling and interruption to the blood flow.

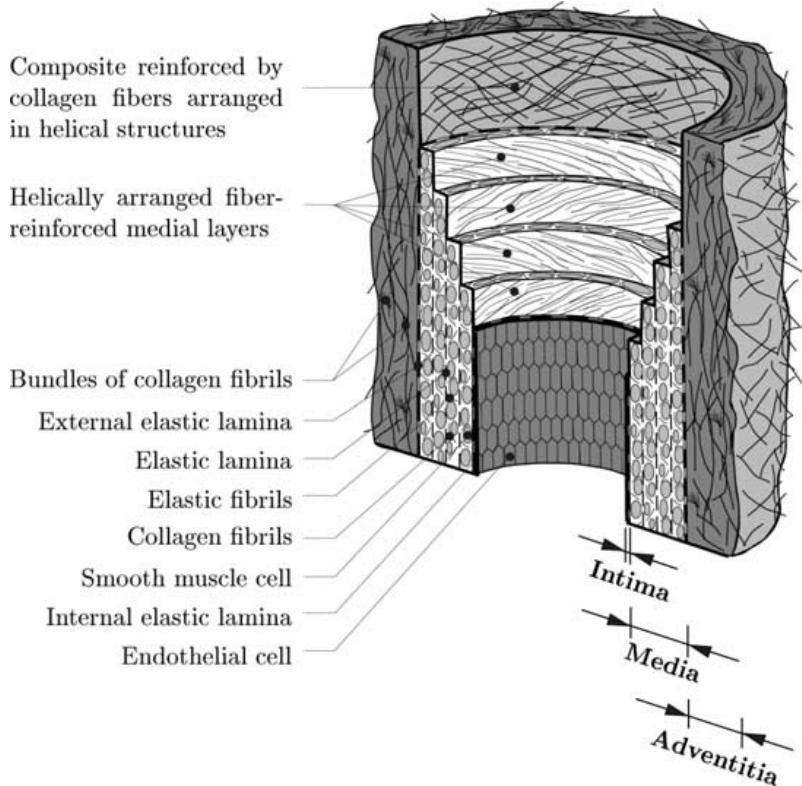


Figure 4-3a Artery wall mechanical structure – collagen and elastin fibrils.

Holzapfel et al 2000 J Elasticity

The second example sheet asks you to derive the following expression for capacitance, which assumes that the vessel does not lengthen, that the wall is a linear elastic material with Young's modulus E and wall thickness t :

$$C = \frac{3\pi a^3 L}{2tE}$$

where the material is assumed to have a Poisson's ratio of 0.5, relating to an incompressible material. We thus get the equivalent circuit shown in Figure 4-4. The values of resistance, inductance and capacitance for all the different types of vessels for Table 4.2 will be calculated on the example sheet.

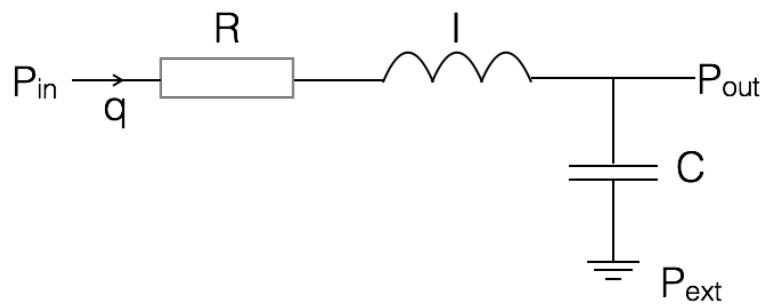


Figure 4-4 Equivalent circuit for blood flow

Table 4.2: Resistances, inductances and capacitances of major blood vessels

	Arteries (Aorta)	Arterioles	Capillaries	Venules	Veins (Vena cavae)
Resistance (mmHg/(l/s))					
Inductance (mmHg/(l/s ²))					
Capacitance (l/mmHg)					

These lumped parameter models are subject to several limitations. In particular, the vessel wall does not deform with infinitesimal strains as required for linear elastic theory, is not thin and also is not a passive linear elastic material. The relationship between pressure and volume is more similar to an exponential rise than a straight line. Although this can be modelled using a capacitance that varies with pressure, the model then becomes non-linear and considerably harder to analyse. A quick survey of the published literature will yield a number of highly complex models.

Although we have only considered a single vessel, larger networks of vessels can be built by adding the equivalent circuits in series and parallel as necessary. It is common to simplify the larger networks by neglecting some resistances and capacitances and merging others. This requires some knowledge of the physiology and a number of assumptions. The simplest realistic equivalent circuit model of a body organ comprises five components (a significant reduction), as shown in Figure 4-5, which you will validate in the example sheet. The simplest model of the systemic circulation then becomes a series of organs in parallel, where each body organ is supplied by the aorta and drains into the venae cavae.

The compliance of the arteries is vital in converting the pulsatile nature of the flow exiting the heart into a steady constant flow. During systole, the flow of blood into the arteries is greater than that exiting into the arterioles, so the arteries expand, contracting during diastole. There is a storing of energy during the first stage, which is then used to propel the blood forward during the second stage. By the time that the flow has reached the capillaries, the flow velocity is approximately constant, as will be shown in the example sheet (question 7).

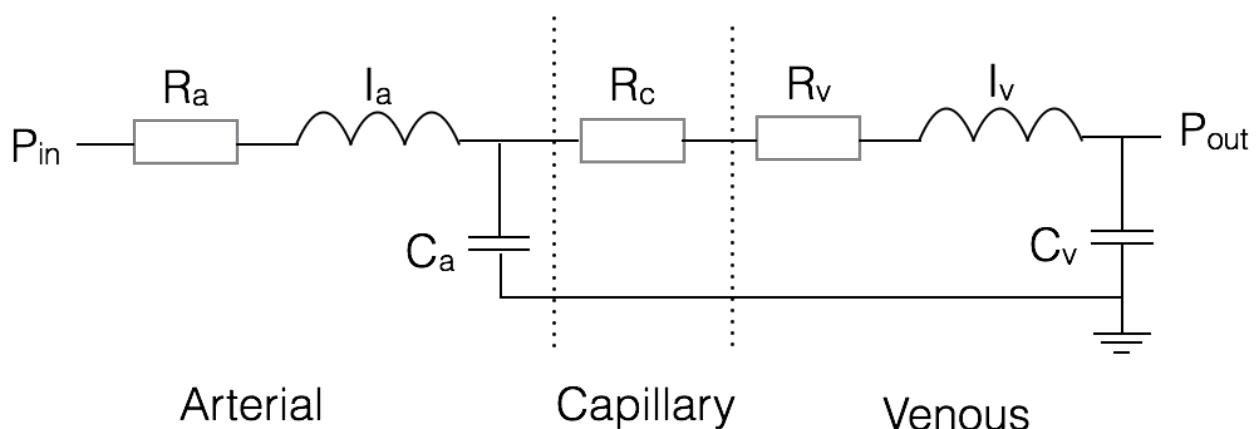


Figure 4-5 Approximate equivalent circuit for single body organ

4.4 Perfusion

An important function of the circulation is to support metabolism by supplying nutrients and removing waste. Thus we are often interested at the capillary level less in blood flow and more in terms of blood supply or **perfusion**. Perfusion measures the rate of delivery of blood to a volume of tissue, rather than simply the flow rate through the vessels; thus it has units of volume of blood per volume of tissue per unit time, typically ml blood/ml tissue min⁻¹. As we will see later in the course delivery and removal of gases is essentially perfusion limited because it is happening over the large surface area of the capillary bed, i.e. it is perfusion that determines how much is delivered and taken away.

A number of very widespread diseases arise due to reduced perfusion, called hypoperfusion. Normally this occurs due to a blockage further upstream in the arteries, for example, both (ischaemic) stroke and heart attacks are due to areas of the brain or heart respectively receiving less blood than is required. In selecting appropriate therapies, the measurement of perfusion and the use of medical imaging techniques to generate perfusion maps of organs are highly important. These methods all rely on some form of contrast agent to act as a tracer. For example, Positron Emission Tomography might employ radiolabelled (i.e. emits radioactivity that can be sensed by a detector) water or Magnetic Resonance Imaging might use a Gadolinium based compound. In each case the contrast agent can be ‘seen’ by the imaging device and its arrival and accumulation or passage through the tissue used to quantify perfusion. This quantification will be done using tracer kinetics that follows much the same principles we looked at in lecture 5. Although now our compartment will typically be a small volume of tissue.

4.5 Blood pressure

Blood pressure is conventionally taken to mean the Arterial Blood Pressure (ABP), which is the pressure found in the arteries and their branches. The blood pressure is a waveform (Figure 4-6) varies from a high pressure, caused by ventricular contraction, which is termed systolic, as it occurs during systole, to a low pressure, termed diastolic, as it occurs during diastole. Note that the rise is much sharper than the subsequent fall, and the presence of the 'dicrotic notch' that occurs when the aortic valve closes. The heart rate can be calculated from the blood pressure waveform, in a similar manner to the method used in the ECG.

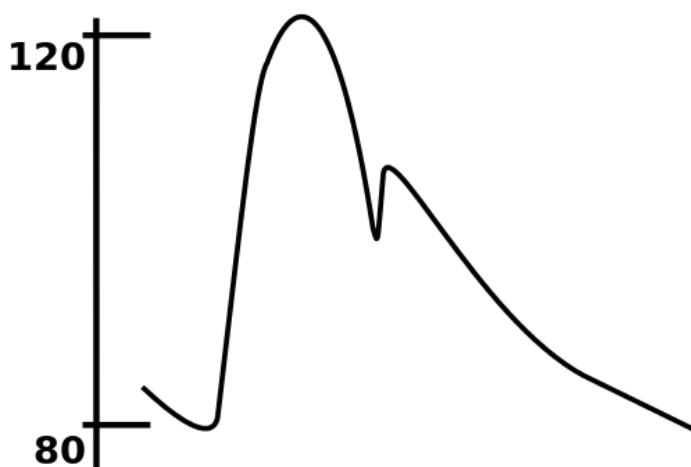


Figure 4-6 Arterial blood pressure waveform (units are mmHg)

By Benutzer:Lupino at de.wikipedia (Public domain), from Wikimedia Commons

Normally, only the systolic and diastolic blood pressure are measured for each heart beat and recorded in the form systolic over diastolic. They are conventionally measured in millimetres of mercury (mmHg), rather than in Pa. The blood pressure reading from Figure 4-6 would thus be 120/80, representing 120 mmHg systolic and 80 mmHg diastolic. The Mean Arterial Pressure (MAP) is also of interest, since it gives the average effective pressure that drives blood

through the systemic circulation. Often only the systemic and diastolic values are known and these are used in a weighted sum to estimate MAP:

$$MAP = \frac{2 DBP + SBP}{3}$$

where SBP and DBP represent systolic and diastolic blood pressures respectively. This approximation to MAP (which would require integration of the full pressure waveform for more accuracy) is reliable under normal conditions.

To understand the blood pressure values, we can consider the mean arterial pressure to be related to the Cardiac Output (CO) and the Total Peripheral Resistance (TPR):

$$\frac{MAP}{CO} = TPR$$

where we have assumed that the central venous pressure is approximately zero. Any changes in MAP must thus be due to changes in CO or the resistance of the vascular network.

Another measure that is commonly used is the Arterial Pulse Pressure (APP), which is simply defined as:

$$APP = SBP - DBP$$

i.e. the difference between the maximum and minimum value of arterial pressure over the course of each heart beat. We can approximately relate the change in pressure with the change in volume (i.e. the stroke volume) and the arterial compliance:

$$APP = \frac{SV}{C_a}$$

Any changes in APP must thus be due to changes in the stroke volume of the heart or the compliance of the vascular network. To derive this equation, we assume that no blood leaves the arterial system during cardiac ejection. The mean arterial pressure and pulse pressure are thus more useful measures of the performance of the cardiovascular system than the systolic and diastolic blood pressures.

4.5.1 Non-invasive measurement techniques

Blood pressure is measured non-invasively using a sphygmomanometer, which consists of an inflatable cuff that is placed around the upper arm over the brachial artery and connected to a pressure gauge. Since the pressure gauge is usually a column of mercury, blood pressure is measured most easily in millimetres of mercury. The cuff is inflated to a pressure well above the systolic pressure (in the region 175-200 mmHg): since this is higher than the highest arterial pressure, the blood vessels collapse, preventing blood flow to or from the forearm. A stethoscope is then placed over the artery just below the cuff and the cuff pressure allowed to fall gradually: as soon as the cuff pressure falls below the peak arterial pressure, some blood passes through the arteries, but only intermittently. This is the SBP.

Since this flow is turbulent and intermittent, tapping sounds are produced, known as Korotkoff sounds. As the pressure continues to drop, the sounds increase in volume before decreasing again. The pressure at which the sounds disappear completely is the DBP. Since these sounds are often difficult to hear near the diastolic pressure, accurate determination of the DBP is often a matter of

experience. This technique is known as the auscultatory technique, since it is based on listening to sounds.

It is also possible to use oscillometry to measure blood pressure. This is performed using a cuff with an in-line pressure sensor. Again, the cuff is pressurised above SBP and allowed to deflate: the measured cuff pressure is high-pass-filtered above 1 Hz to observe the pulsatile oscillations as the cuff deflates. The point of maximum oscillation corresponds to a cuff pressure equivalent to MAP. Both SBP and DBP are found where the amplitude of the oscillations is a fixed percentage of the maximum amplitude: 55 % for SBP and 85 % for DBP. Figure 4-7 shows some example waveforms.

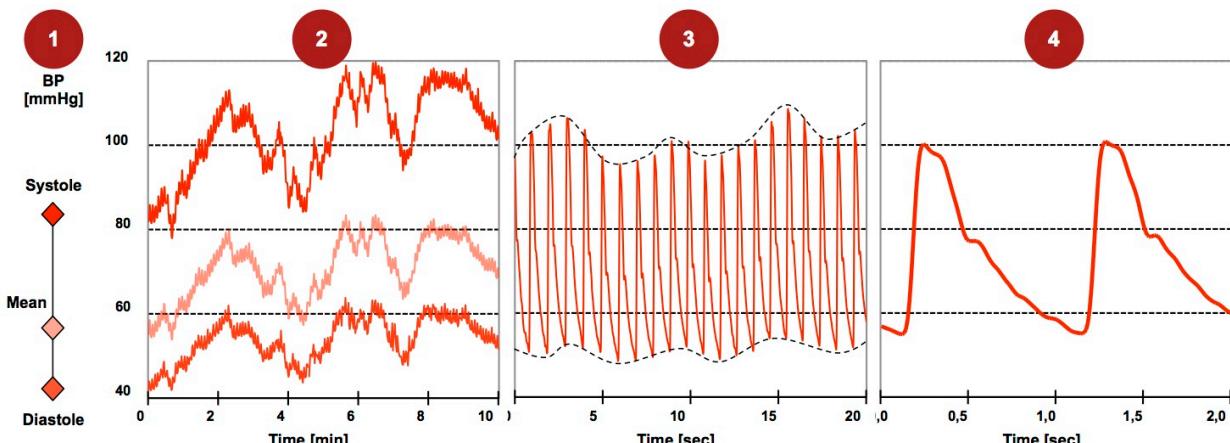


Figure 4-7 Example waveforms recorded during oscillometric blood pressure measurement shown over different time scales of measurement

By ProfBondi under [CC-BY-SA-3.0](#), via Wikimedia Commons

4.5.2 Invasive measurement techniques

However, these non-invasive methods are used for irregular samples. Continuous measurement of the blood pressure waveform is best provided by invasive techniques, using a cannula to introduce a saline filled catheter directly into a

large artery. The so-called “arterial line” catheter is coupled via a stiff fluid-filled tube to a pressure transducer allowing a direct, continuous measurement of the arterial blood pressure waveform.

4.5.3 Clinical relevance

High blood pressure, also known as hypertension, is usually taken to mean blood pressure of 140/90 mmHg or greater. High blood pressure is associated with increased risk of a number of serious and potentially life-threatening conditions, including heart disease, stroke, aortic aneurysm and kidney disease. Pharmacological therapies for hypertension include calcium channel blockers and ACE inhibitors, and targets include cardiac muscle and the vascular smooth muscle. The contraction or “tone” of the smooth muscle directly regulates blood flow.

5 The respiratory system

The respiratory system can roughly be divided into the upper airways in the head and neck, and the lower airways including trachea and all the structures in the lungs. The primary functions of the respiratory system are:

- Gas exchange – the movement of O₂ into the body and CO₂ out.
- Host defence – provides a barrier between the outside world and the body.
- Synthesis and metabolism of various compounds.

5.1 The lungs

The lungs are contained in a space with a volume of approximately 4 litres but present a surface area of approximately 85 m² for gas exchange. This is achieved through a highly branched structure, Figure 5-1, the trachea branches into the two main stem bronchii which themselves divide into further bronchii at progressively small diameters. Subsequently further generations of the branches are called bronchioles which finally terminate in the alveoli after approximately 23 bifurcations. Both the smallest bronchioles and alveoli are involved in respiration over a gas-blood barrier that is only 1-2 µm thick. The pulmonary capillary bed is the largest in the body having a surface area of approximately 70-80 m². The capillary volume of the lungs is 70 ml at rest, but can increase up to 200 ml during exercise. This is achieved through both the recruitment of closed vessels or compressed capillary segments and the enlargement of all capillaries due to an increase in pulmonary pressure when cardiac output is increased.

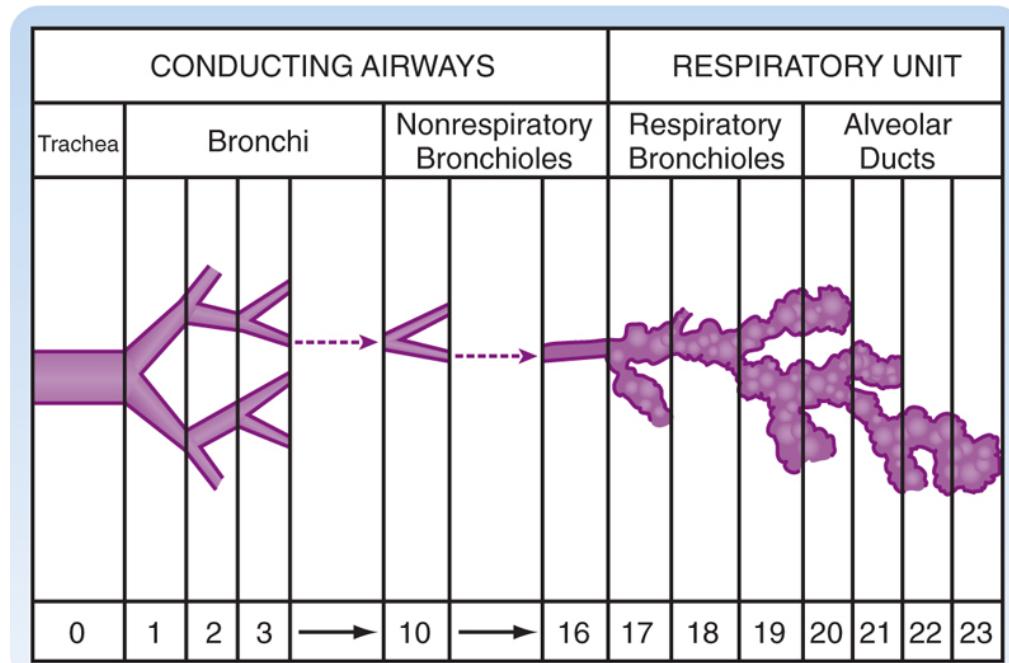


Figure 5-1: Branching structure of the lungs, with bifurcation number [Berne & Levy]

Figure 5-2 shows the breathing cycle. This is mainly achieved by the action of the diaphragm, although the external intercostal and scalene muscles in the chest also play a role. Air is drawn into the lungs by an increase in the chest cavity volume, pushing the abdominal contents downwards. Exhalation occurs passively during normal breathing, but may involve active effort by muscles during exercise and hyperventilation.

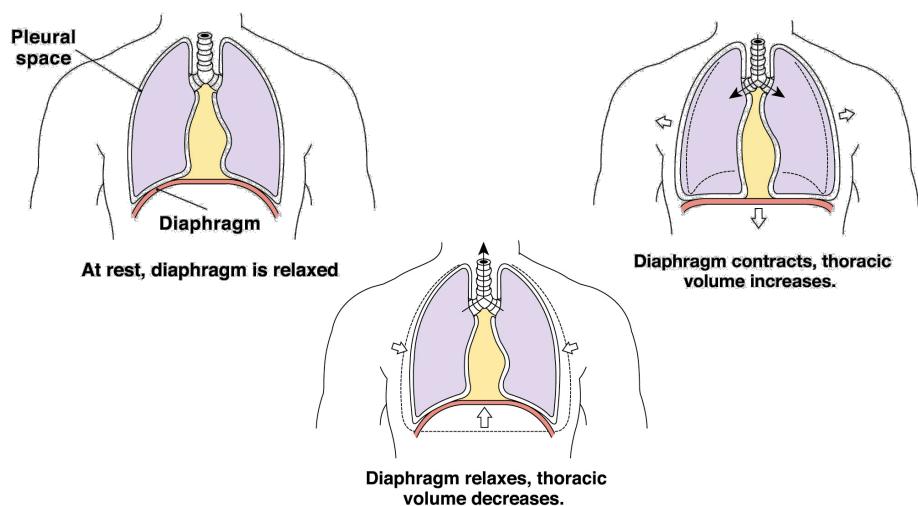
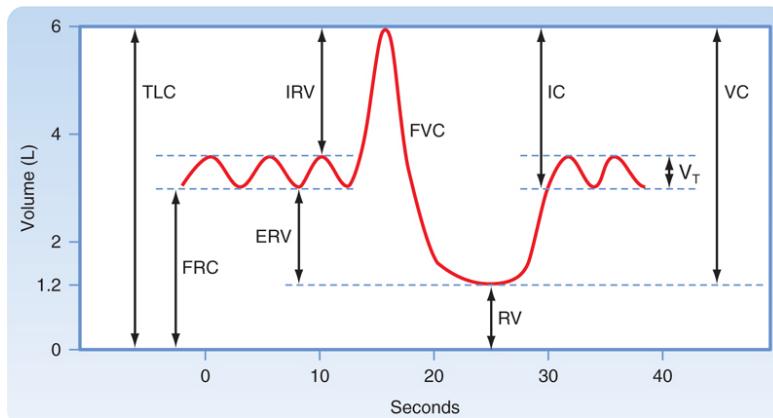


Figure 5-3: Breathing cycle [Berne & Levy]

The total lung capacity is the total volume of air that can be contained within the lung. Various other volumes and capacities can be defined as shown in Figure 5-4, where capacities are composed of two or more volumes. Under normal breathing only a relatively small range of the available lung volume change is used.



ERV, expiratory reserve volume;
FRC, functional residual capacity;
FVC, forced vital capacity;
IC, inspiratory capacity;
IRV, inspiratory reserve volume;
RV, residual volume;
TLC, total lung capacity;
VC, vital capacity;
 V_T , tidal volume.

Figure 5-4: Definition of the various lung volumes and capacities [Berne & Levy]

5.2 Gas transport

Air is a mixture of various gases predominantly nitrogen (78%) with a large proportion of oxygen (21%). We often refer to the partial pressures of each of the components, where the partial pressure of gas i , is defined by:

$$p_i = x_i P$$

where x_i is the mole fraction of the gas and P is the total pressure of the gas mixture. So the partial pressure is effectively the pressure that this gas would exert if it alone were present. In the following we will consider only one gas, using $p \equiv p_i$.

Since in the lungs gases are (indirectly) in contact with a liquid, the blood, we need to be able to relate partial pressure of a gas to its concentration in the blood. We can do this via Henry's law:

$$c = \sigma p$$

where σ is the Ostwald solubility co-efficient, typical values for respiratory gases in plasma are given in Table 5.1.

Table 5.1: Solubility of respiratory gases in blood plasma

Gas	σ (mM/mm Hg)
O ₂	1.4x10 ⁻³
CO ₂	3.3x10 ⁻²
CO	1.2x10 ⁻³
N ₂	7x10 ⁻⁴
He	4.8x10 ⁻⁴

A simple model for the transfer of gas across the capillary-alveoli interface assumes that the flow is linearly proportional to the difference in partial pressures, thus:

$$q = D_s \left(p - \frac{c}{\sigma} \right)$$

where q is the net flux per unit area and D_s is the surface diffusion coefficient. This is a very similar result to the case of diffusion of a species through a membrane, where D_s here is taking the role of permeability. On the example sheet you will investigate the gas flux across the wall of a simple cylindrical capillary that is in steady state. In the limit the expression for gas flux reduces to:

$$Q = f\sigma(p - p_{in})$$

where p_{in} is the partial pressure of the gas in the blood at the inlet to the capillary. Thus the gas flux depends only upon the pressure difference and the blood flow rate, f . This only holds as long as the permeability of the membrane

to the gas (i.e. the D_s value) is sufficiently high, which is primarily achieved in the lungs through having very a thin membrane. Since the gas flux depends on blood flow and not the rate of diffusion it is called perfusion limited.

Whilst the analysis above hold for the inert gases where Henry's law holds. The metabolic gases are more complicated. CO_2 is mainly transported within the red blood cells as HCO_3^- , the reaction being catalysed by the enzyme carbonic anhydrase:



where CO_2 combines with water to form carbonic acid, which then produces bicarbonate (HCO_3^-) and H^+ . The equilibrium constant for the second part of the reaction is given by:

$$K_A = \frac{[\text{HCO}_3^-][\text{H}^+]}{[\text{H}_2\text{CO}_3]}$$

and since it is assumed that the concentration of CO_2 is very similar to that of H_2CO_3 , i.e. pretty much all the available CO_2 converts to carbonic acid, it can be written as a 'corrected' equilibrium constant:

$$K_A = \frac{[\text{HCO}_3^-][\text{H}^+]}{[\text{CO}_2]}$$

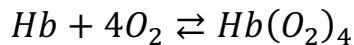
It is possible (but we won't derive this) to evaluate what difference this makes to the removal of CO_2 from the capillary blood in the lungs and arrive at the result:

$$Q = f(1 + K_A)\sigma_{\text{CO}_2}(p_0 - p_{\text{CO}_2})$$

which is $(1 + K_A)$ larger than our result for inert gases above, with $K_A = 20$ at a normal pH of 7.4 (see below). The conversion of CO_2 to bicarbonate thus effectively increases the flow rate, because as CO_2 leaves the capillary by diffusion from the plasma it is rapidly replenished by more from the reversal of the

bicarbonate reaction. Thus this is an example of facilitated diffusion, which occurs when the flux of a chemical is amplified by a reaction that takes place in the diffusing medium.

We have already seen in the first part of the course that oxygen binds to haemoglobin (Hb) in the blood:



This is the primary means by which it is transported; a negligible fraction (3%) is carried in solution in the plasma. Figure 5-5 shows the relationship between the partial pressure of O₂ and haemoglobin saturation which is highly non-linear. In theory the enhancement provided by Hb on oxygen transport could be as much as 200, but in practice enhancement around 32 is achieved.

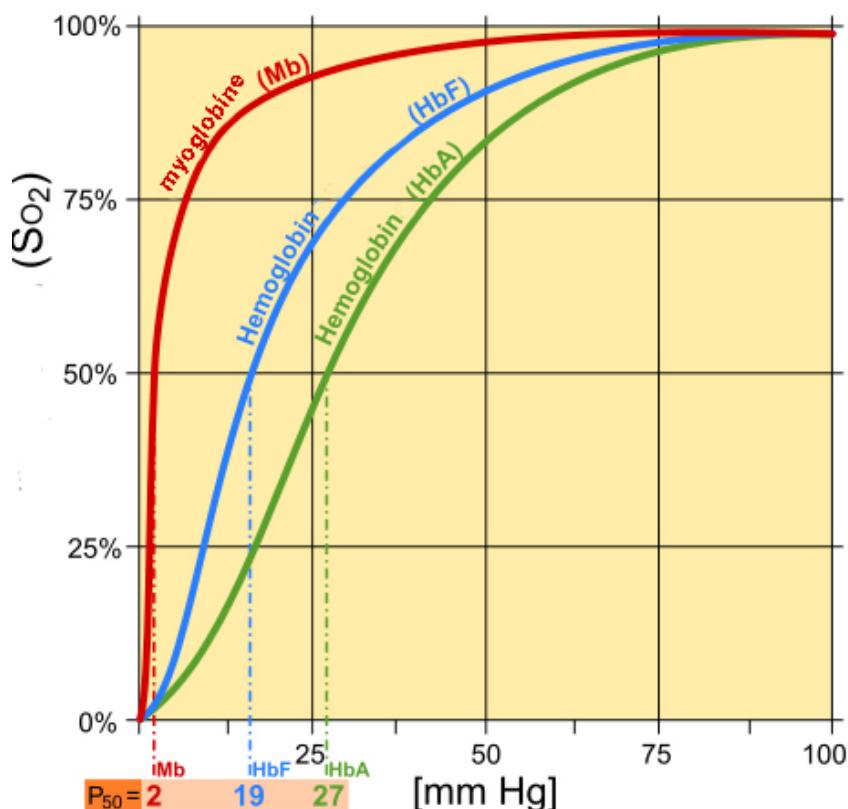


Figure 5-5: Saturation curves for haemoglobin (adult – HbA, fetal – HbF) and myoglobin. [Berne & Levy]

Delivery of gases to the tissues is essentially the reverse of the process in the lungs, and again the process is typically assumed to be perfusion limited. We can thus equate the amount of gas delivered to the difference in partial pressure between the arterial and venous ends of the capillary bed. This process can be modelled by a linear first order differential equation:

$$\frac{dp_t}{dt} = f \frac{\sigma_b}{\sigma_t} (p_a - p_v)$$

where p_a , p_v , and p_t are the partial pressure in arterial blood, venous blood and tissue respectively, and we have to consider the solubility of the gas in the blood and tissue. This means that gas delivery can be thought of like the one-compartmental models we considered when we examined pharmacokinetics. In this case the compartment is the tissue into which gas is being delivered and we assume that there is no spatial variation in the partial pressure in the tissue, thus the compartment is referred to as 'well stirred'. This can be represented graphically as in Figure 5-6, where a number of other simple models of tissue-capillary gas exchange are shown.

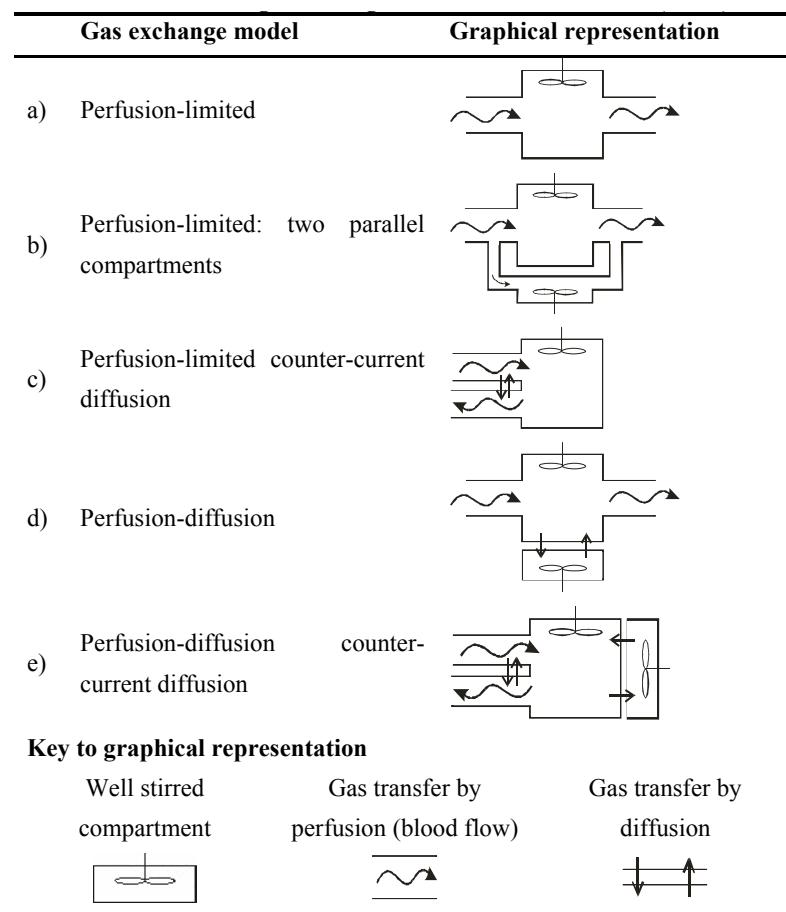


Figure 5-6 Compartmental models of tissue gas exchange.

The one compartment model means that the tissue concentration will respond exponentially to a change in gas concentration and a time constant can be determined for that process, often the half-life is quoted. This will vary from tissue to tissue depending upon the surface diffusion constant, but more significantly upon the perfusion rate. Given the range of tissues and accompanying perfusion rates simple models often divide the body into a collection of compartments with a range of representative time constants.

This description is fine for the inert gases, but is insufficient for the metabolic gases. As we have already seen, binding in the blood gives a non-linear relationship between concentration and partial pressure. There is further binding of oxygen in the tissues to myoglobin (Mb), whose saturation curve is much like

the standard Michaelis-Menten function not the sigmoidal shape of haemoglobin, Figure 5-5. The difference between these two curves arises from the greater affinity of myoglobin for oxygen which means oxygen is readily transferred from Hb to Mb, improving the transfer rate from blood into tissue. The presence of Mb in muscles also provides some limited oxygen store and also accounts for the red colour of red meats.

A further aspect for the metabolic gases is that oxygen is consumed in the tissues whilst carbon dioxide is being produced, requiring an additional metabolism term in the equation above. Because oxygen is rapidly metabolised (or bound) it is often a reasonable approximation to assume zero dissolved oxygen in tissue and an equivalent fixed fraction for the CO₂ that has been produced, if we are interested in the total pressure of gas in solution in the tissue.

5.3 Control of acid-base balance

One further aspect of the body's behaviour that we will consider here is the regulation of the acid-base status. The maintenance of the pH of arterial blood between 7.35 and 7.45 is absolutely vital for the correct functioning of the human body. The most important influence on pH is the transport of CO₂ in the blood. The reaction equation that governs buffering is the same one we considered for CO₂ transport above. The expression for the 'corrected' rate constant can be rearranged into the form:

$$pH = pK_A + \log_{10} \left(\frac{[HCO_3^-]}{[CO_2]} \right)$$

where $pH = -\log_{10}[H^+]$ and $pK_A = -\log_{10}[K_A] = 6.1$. This is the Henderson-Hasselbach equation. The concentration of CO₂ is approximately proportional to the partial pressure of CO₂. The physiological importance of this balance may be

seen in the fact that the concentrations of both bicarbonate and carbon dioxide can be independently controlled, by the kidneys and the lungs respectively.

6 Nervous system

We have so far looked at a number of the most vital systems in the body. However, their actions and interactions all need to be coordinated and this role falls to the nervous system. The nervous system can be modelled conceptually as in Figure 6-1. Here it has been broken down by information flow and whether we are conscious of the information or not. The nervous system can be divided into two parts:

- The central nervous system (CNS): the brain and spinal cord.
- The peripheral nervous system (PNS): nerves (bundles or nerve cells) connecting the CNS to other parts of the body. The PNS also encompasses the enteric nervous system, a semi-independent part of the nervous system responsible for the gastrointestinal system.

Notice also that the model is divided up into efferent (input) and afferent (output) paths depending upon whether information is brought in to or taken out of the CNS. As well as direct ‘point-to-point’ signalling achieved via nerves, the nervous system also has a mechanism for ‘broadcast’ signalling through the release of hormones.

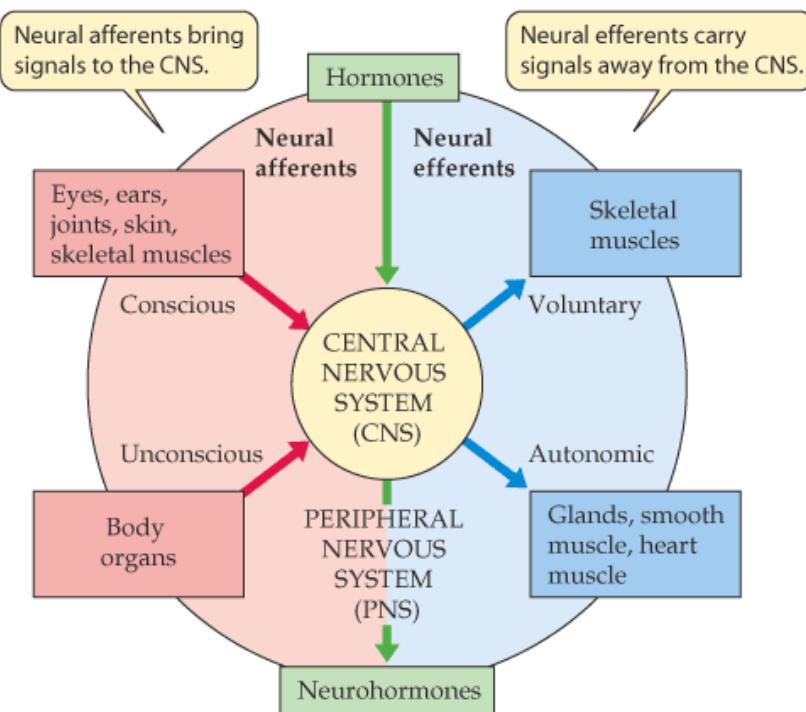


Figure 6-1: Conceptual diagram of the nervous system. [Berne & Levy]

6.1 Neurons

We have already met the idea of a neuron or nerve cell in the first part of the course where we considered the action potential and chemical synapses. A number of specialized neurons exist:

- Sensory neurons: respond to stimuli such as light and sound in the sensory organs and send this information back to the CNS.
- Motor neurons: receive signals from the CNS and cause muscle contraction or affect glands (for the release of hormones).
- Interneurons: connect neurons to other neurons within the same region of the CNS.

Typically a neuron will have a cell body, dendrites and an axon. The dendrites are thin structures arising from the cell body that typically branch multiple times forming a complex 'dendritic tree'. In contrast the axon (and there is only ever

a single axon) is a special extension of the cell body that may extend as far as 1 meter. The axon itself may branch hundreds of times before it terminates in a synapse at the dendrite of another neuron. At the majority of synapses signals are sent from the axon of one neuron to the dendrite of another, although there are exceptions to this rule. It is the axon that carries signals over long distances and is thus insulated with a myelin sheath that in turn is interrupted at various points by the nodes of Ranvier to boost conduction of the action potential.

6.1.1 The Patellar Reflex

Reflexes are rapid involuntary movements made in response to a stimulus. They can provide information to a clinician on the integrity of the central and peripheral nervous system. Reflex arcs, the neural paths linking the external stimulus reception and the response motor signal, do not pass through the brain. Tendon reflexes are part of the musculoskeletal control system, providing rapid responses to changing tendon stretch. The patellar (knee-cap) reflex (Figure 6-2) is well known but there are several others. A rapid stretch in the patellar tendon e.g. by tapping with a tendon hammer is detected by stretch sensitive sensory neurons in the muscle (also sensitive to time derivative and second derivative of stretch). The signal in the sensory neuron arrives at the spinal cord at a synapse with a motor neuron, in a dorsal root ganglion. This then elicits an action potential in the motor neuron, which is carried back to the quadriceps muscle arriving at a neuromuscular synapse we met in lecture 4. The resulting AP causes contraction of the muscle fibre, which when repeated across the whole muscle causes contraction of the quadriceps muscle and the resulting leg extension with a latency of a few 10s of ms following patellar stretch. A second inhibitory synapse also ensures the antagonistic muscle is relaxed.

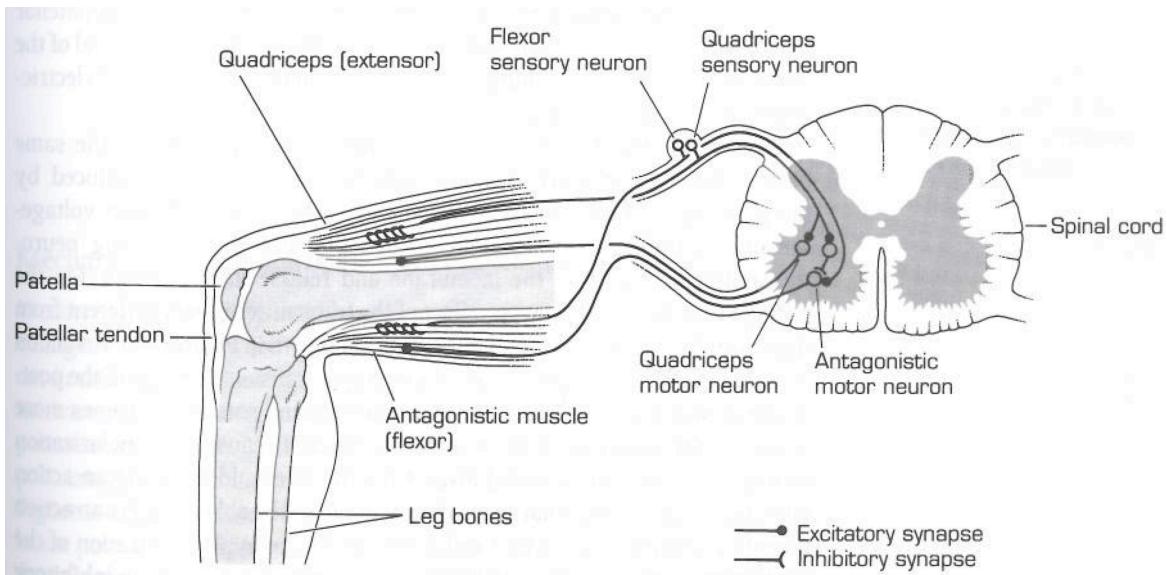


Figure 6-2: Patellar reflex [Matthews p137]

6.2 Temporal and spatial summation of synaptic potentials

The neuromuscular junction is unusual in one respect, that a single AP that arrives at the presynaptic side leads to a sufficiently large depolarization on the post synaptic side to trigger an AP there. Thus such a synapse is called a 'one-for-one' synapse. However, most synapses are not that strong: a single presynaptic AP will cause only a small depolarization of the postsynaptic cell, called a excitatory postsynaptic potential (epsp). The synapse between a single stretch receptor and the quadriceps motor neuron in the patellar reflex is a typical example of this. Each epsp is of the order of 1 mV, far smaller than the 10-20 mV threshold required. However, if several subsequent epsp arrive within a few ms, before the previous potential has decayed, a sufficient depolarization of the postsynaptic cell can be achieved. This is called **temporal summation**. An alternative mechanism by which epsp can sum to reach threshold is via the postsynaptic cell receiving multiple simultaneous presynaptic inputs, this is called **spatial summation**. This relies on the fact that most neurons are connected to

many other via their dendrites. Both temporal and spatial summation are involved in the patellar reflex.

6.3 Excitatory and Inhibitory synapses

So far we have only met excitatory synapses where the AP in the presynaptic cell causes a depolarization in the postsynaptic cell. However, it is also common to find inhibitory synapses, where the release of neurotransmitter due to the presynaptic AP tends to prevent the firing of the postsynaptic AP. In this case the neurotransmitter causes a **hyperpolarization** of the post synaptic cell, making the membrane potential more negative and moving it further way from the threshold required to elicit an AP. Thus we now also have a class of **inhibitory postsynaptic potential** (ipsp). Like the epsp we have already met, the ipsp is achieved through changes in the ionic permeability of the postsynaptic cell membrane. One possible mechanism for this would be an increase in the permeability to K⁺ similar to the undershoot we saw at the end of the AP in lecture 3. Many inhibitory synapses, however, rely on changes in Cl⁻ permeability. In many neurons chloride pumps maintain the chloride equilibrium potential more negative than the membrane potential, thus an increase in Cl⁻ permeability leads to a hyperpolarization of the neuron. Even when the Cl⁻ equilibrium potential is near to that of the membrane potential inhibition can occur, as although there will be no appreciable hyperpolarization the increase in Cl⁻ permeability will resist any increases in the membrane potential brought about by an excitatory input.

The combination of inhibitory and exhibitory synapses plays an important role in the patellar reflex. In Figure 6-2 as well as the quadriceps muscle we also have to consider the flexor muscles at the back of the thigh. As the leg extends this will cause a stretch in these muscles that in turn would, via the excitatory

pathway through the spinal cord, cause contraction of the flexor muscle, jerking the leg back again. In turn this would elicit a stretch and contract reaction from the quadriceps muscle and so it would go on. However, the inhibitory link between quadriceps sensory neuron and the flexor's motor neuron prevents this occurring and only the first extension is seen.

6.4 Autonomic nervous system

So far we have considered the voluntary side of the peripheral nervous system by looking at the control of the skeletal muscles, this is often referred to as the **somatic nervous system**. However, there are many on-going motor activities that are coordinated by the nervous system. These include regulation of digestion, maintain glucose balance and regulating heart rate. This part of the nervous system is called the **autonomic nervous system** and unlike the somatic nervous system there is not a direct neural link between the CNS and the cells that respond. Instead the cell bodies of neurons in the autonomic system reside in **autonomic ganglia** that are distributed around the body. The CNS controls these ganglia by way of output neurons whose cell bodies lie in the CNS. Additionally, whereas in the somatic system the target cells are only ever in receipt of excitatory signals, the autonomic system is divided into **sympathetic** and **parasympathetic** parts. Most organs receive signals from both and broadly the role of the sympathetic system is to put the organ into 'emergency mode', whereas the parasympathetic system has the opposite effect of placing the organ into 'vegetative mode'.

6.4.1 Autonomic control of the heart

The heart is a good example of the competing role of sympathetic and parasympathetic nerves:

- Parasympathetic input: synaptic terminals release the neurotransmitter ACh, this slows the rate of depolarization during the pacemaker potential of the SA node. Thus increasing the interval between successive APs, slowing the heart rate. ACh acts by increasing potassium permeability, keeping the membrane potential nearer to that of potassium, retarding the growth of the pacemaker potential toward the threshold for triggering an AP.
- Sympathetic input: synaptic terminals release norepinephrine. This speeds the heart rate and increases the strength of contraction, an effect which is mediated by an increase in calcium permeability. The greater the number of calcium channels that are open the lower the threshold is for triggering an AP in the SA, thus increasing the heart rate. In the cardiac muscle cells the increase in calcium permeability increases the calcium influx during the plateau, increasing the strength of contraction.

In both cases the effects of the neurotransmitter are indirect, unlike those we saw when we looked at chemical synapses where the neurotransmitter acted directly on the ion channels. For more information about this see Matthews, for our purposes we will simply note that this means the body can via an indirect mechanism effect longer term changes without having to provide a continuous neural signal.

6.5 The Brain

The ‘pinnacle’ of the nervous system is the brain, where many millions of individual neurons interact via a complex network of dendritic connections and synapses. The brain itself is can broadly be considered to contain both ‘grey matter’ and ‘white matter’ reflecting different visual qualities of the tissue. The grey matter, mainly containing cell bodies and few myelinated axons, forms a

thin layer with large surface area that takes on the form of a highly folded sheet within the head. The white matter is composed of bundles of myelinated axons from neurons carrying APs to different regions of the brain and out of the brain. Within the brain there are also glial cells which support the neurons structurally and metabolically.

The complexity of the brain makes it both difficult to study and at the same time one of the most studied organs. Non-invasive methods include electroencephalography (EEG) that measure electrical signals in the brain using an array of electrodes placed on the head. Magnetoencephalography (MEG) can be used to detect magnetic fields arising from electrical activity of the brain with highly sensitive magnetic detectors. Both methods provide very highly sampled temporal information about signals in the brain, but provide low spatial resolution, since it is difficult to reconstruct spatial locations from an array of measurements made outside of the head. Magnetic Resonance Imaging (MRI) methods have also been used extensively to study the brain. Functional MRI (fMRI) exploits the Blood Oxygen Level Dependent (BOLD) effect that relies upon the different magnetic properties of deoxygenated blood, allowing increases in oxygen usage to be indirectly measured in the brain during a task compared to that during rest. This method provides spatial resolution of the order of mm, but with poor temporal resolution, typically one measurement every few seconds. Diffusion tensor MRI maps the mobility of water molecules within each voxel, with diffusion enhanced along structural features such as axon bundles. This technique is sensitive to the early changes in tissue following a stroke, and has also been used to generate a map of the so-called human connectome
<http://www.humanconnectomeproject.org/>