Lecture 5: The determinants of cardiac output

It is important to regulate **cardiac output (CO)**. It needs to be sufficient to ensure adequate perfusion of all the tissues, which means it must increase as metabolic demands rise in exercise, for example. Cardiac output is also critical in the determination of **arterial blood pressure (ABP)**, as we'll see in the next lecture. This lecture explains the underlying physical determinants of cardiac output. It is important to understand these concepts in order to appreciate how CO and ABP can be controlled.

The heart has surprisingly little control over CO!

In a classic experiment, Guyton *et al*. (1957) effectively replaced the hearts of dogs with high-output pumps (Figure 1). Reducing the pumping capacity below normal reduced cardiac output, as you might expect. However, perhaps surprisingly, *increasing the pumping capacity did not increase cardiac output*:

This experiment illustrates two important circulatory concepts:

1) The heart is *necessary* to maintain CO, *but*
2) The heart *does not normally limit* CO.

So why can't an increase in heart pumping capacity *on its own* increase CO? The answer is:

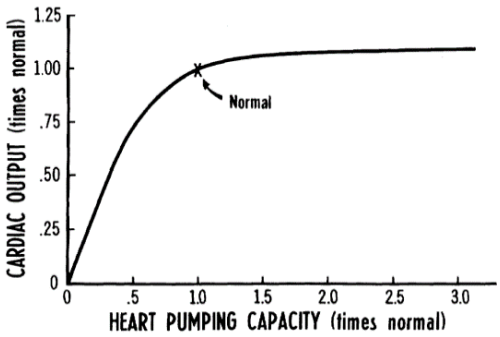

Figure 1: replacement of a dog's heart with a high output pump does not, by itself, increase cardiac output; though decreased pumping capacity does reduce cardiac output. Guyton *et al*, 1957.

The circulation is a closed system.

Imagine a pump *entirely within* a fluid-filled balloon. It can move fluid within the balloon, but it can't change the average pressure in the balloon, and it certainly can't inflate or deflate it. This is a *closed system*. The circulation is surprisingly similar, as shown in Figure 2.

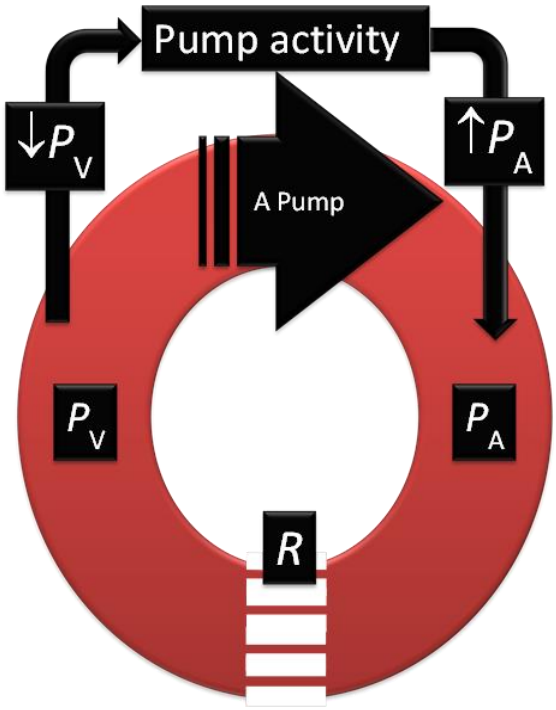

Figure 2: a simple diagram of the circulation as a closed system in which a pump moves blood from veins to arteries, producing a pressure gradient from arteries (P_A) to veins (P_V) driving flow across a resistance *R*.

In this simple model, the heart takes blood from the veins (reducing venous pressure, P_V) and puts it in the arteries (increasing arterial pressure, P_A). This pressure gradient then drives flow through our model system according to the simple relationship:

$$\dot{Q} = (P_A - P_V) / R$$

(Flow = pressure gradient / resistance)

If the closed system depicted above were made of rigid tubing, greater pump activity could produce ever-increasing pressure gradients and hence flows. However, if the tubing is not rigid – imagine, perhaps, that it is an odd-shaped balloon – then an important constraint appears: **if P_V becomes negative** (with respect to atmospheric pressure) **then the tubing will collapse**. Similarly, real veins

collapse when pressure within them drops more than about 1 or 2 mm Hg below atmospheric pressure.

This is an important result, and provides the explanation for Figure 1. The heart cannot increase the arteriovenous pressure gradient (P_A-P_V) beyond the point at which P_V becomes significantly negative, because if P_V becomes negative, venous collapse limits venous return and hence cardiac output. Direct measurement of right atrial pressure (by inserting a catheter *via* the jugular vein) confirms what Figure 1 suggests: **a healthy heart reduces central venous pressure to almost zero**, even at rest. This means that increasing heart rate or myocardial contractility in isolation – for example, by stimulating the cardiac sympathetic nerves or electrically pacing the heart (Figure 3) – cannot significantly increase cardiac output, *unless* venous return is also increased (in this experiment, accomplished by connecting the aorta to the vena cava).

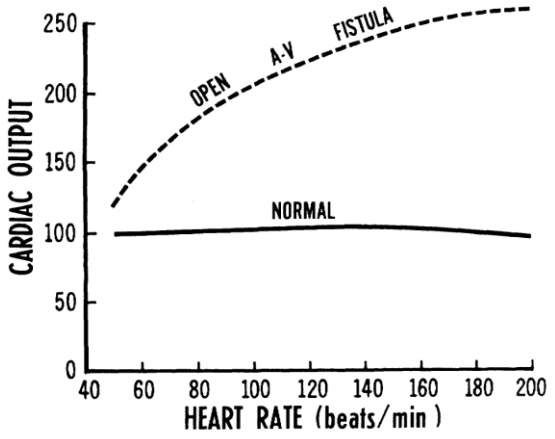

Figure 3: changing the heart rate by electrical pacing does not greatly change cardiac output (solid line, %age of normal). This is because cardiac output is limited by venous return, which cannot be increased by the actions of the heart alone. However, creation of an arterio-venous fistula (dashed line) provides a rapid pathway for blood to return to the heart and reveals that the heart is *capable* of producing a greater cardiac output if venous return is sufficient. Cowley & Guyton, 1971.

This leads to an important question: if increasing cardiac pumping capacity is not *sufficient* to increase cardiac output, what else is necessary?

Mean systemic filling pressure is the main determinant of cardiac output.

In order to increase P_A, the pump *must* reduce P_V. Yet, P_V is normally close to zero and so cannot be reduced. The solution is to raise the mean pressure in the whole system. To see how this works, first imagine that the mean pressure in Figure 2 was zero. This would imply that P_V would become negative as soon as the pump was started, and prevent any flow of blood. Then, imagine that the mean pressure was 10 mmHg. Now, it is possible for pumping to produce a significant arterio-venous pressure gradient *without* collapsing the veins. **The mean pressure determines the *maximum* flow rate** for a given resistance.

Does this apply in real life? Yes: e.g., see Figure 4.

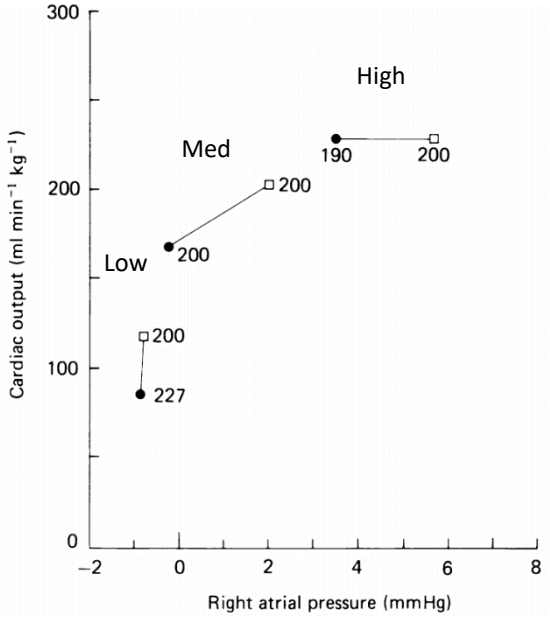

Figure 4: Cardiac output can be increased by increasing the circulating volume (marked low, med, high), and/or by venoconstriction (here caused by splanchnic nerve stimulation in a cat). □ denotes splanchnic stimulation, ● denotes no splanchnic stimulation, and the numbers show heart rate. Barnes, Bower & Rink, 1985. Cardiac output increases when mean systemic pressure is increased (by filling the circulation or constricting the veins), but is not correlated with heart rate.

Mean systemic filling pressure (MSFP) is the mean pressure in the system (equivalently, the pressure that would eventually exist everywhere in the system if the heart stopped). Just as with pressure in a balloon, MSFP can be increased by extra filling (such as a blood transfusion or drinking isotonic fluid) or by constricting the filled volume (imagine standing on a balloon). The latter can be accomplished in real life by venoconstriction,

because about 65-70% of blood is usually in the veins. The effects of these manoeuvres are illustrated by the experiments shown in Figure 4.

Blood volume and mean filling pressure in a real system

It is now time to apply the principles of the simple model system discussed above to the real circulation. However, it is helpful to start by considering a very unphysiological state – an empty circulation.

The normal blood volume in an adult mammal is approximately 70-80 ml/kg of body mass, or about 5 l for a 70 kg person. If this amount of blood is added to an empty circulation, the first ~80% does not cause a rise in pressure, because the pressure stays at zero until the vessel walls begin to stretch. This is called the **unstressed volume** of the circulation: the volume of blood that *just* fills the circulation without stretching the vessel walls.

When the last 20% of normal blood volume is added, the mean pressure in the system will rise. This extra volume is the **stressed volume**, and normally gives rise to a mean pressure of 7 – 10 mmHg in the circulation.

The effect of cardiac activity

Now, consider what happens when the heart starts pumping: blood is transferred from the veins to the arteries. This changes the venous and arterial pressures according to their **compliance**, as shown in Figure 5. Veins are very compliant in the physiological range (although they become quite stiff if very overstretched, as shown by the dashed line in Figure 5; this can be observed when a saphenous vein graft is used to replace a blocked coronary artery.) This venous compliance ensures that if the pressure without cardiac activity was 7 mm Hg everywhere, the reduction in venous pressure with cardiac activity would be relatively small. In contrast, the movement of blood into the far less compliant arteries causes a steep rise in pressure. In the average human, this process continues until venous pressure is close to zero and the mean arterial pressure is about 90-95 mmHg. Notice that this means that when the heart is working normally, the arteries are more filled, and the veins less filled, than they would be if the heart stopped.

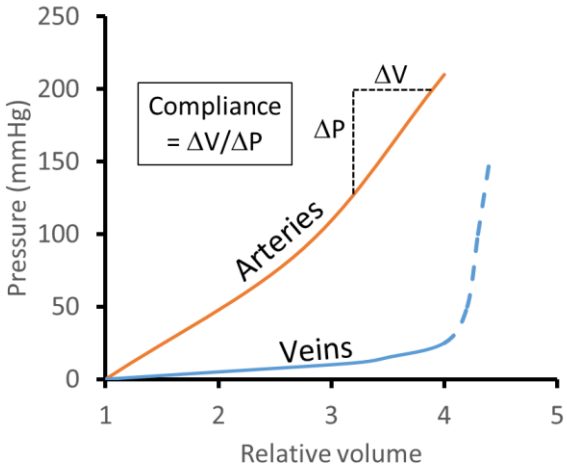

Figure 5: The relationship between volume and pressure in veins and arteries. Volumes are shown relative to the volumes at which the respective vessels are fully relaxed. Note that veins are much more *compliant* than arteries – approximately 10-fold over the physiological range. Thus, when the heart pumps a volume of blood from the veins to the arteries, the pressure in the arteries will rise much more than the pressure in the veins will fall.

This arteriovenous pressure gradient then drives blood flow from the arteries, via the capillaries, to the veins. At last, we have a circulation!

Remember that veins can collapse if the venous pressure falls below atmospheric pressure, so the **maximum arteriovenous pressure gradient is set by the mean filling pressure**. This implies:

1) The heart cannot change the mean pressure;
2) This mean pressure determines the *maximum* cardiac output.

Key abbreviations (and consistent units)

CO	Cardiac Output (l min^{-1})
ABP	Arterial Blood Pressure (mmHg)
TPR	Total Peripheral Resistance (mmHg·$min·l^{-1}$)
MSFP	Mean Systemic Filling Pressure (mmHg)
RAP	Right Atrial Pressure (mmHg)

Quantifying cardiac output

The simple form of Darcy's law states that:

Flow = Pressure gradient / Resistance.

Thus, the arteriovenous pressure difference produces blood flow:

CO = (ABP – RAP) / TPR

Cardiac **O**utput, = (**A**rterial **B**lood **P**ressure – **R**ight **A**trial **P**ressure) / **T**otal **P**eripheral **R**esistance

The arteriovenous pressure gradient (ABP – RAP) is created by the action of the heart, but limited by MSFP. TPR is a "lumped parameter" that treats all the resistances of the various vascular pathways as a single resistance, but is primarily determined by arteriolar resistances. RAP is usually so small compared to ABP that it can often be omitted from the above equation.

Control of cardiac output – Starling's Law

Up to now, we have considered the *determinants* of cardiac output. This gives us a relationship between CO, ABP and TPR that follows simple physical laws, but the *control* of each requires an understanding of the physiology, and in particular the **consequences** of Starling's findings (Starling's experiments were described by Prof Giussani). Note, though, that CO is not directly measured anywhere in the body: rather, it is regulated to maintain ABP.

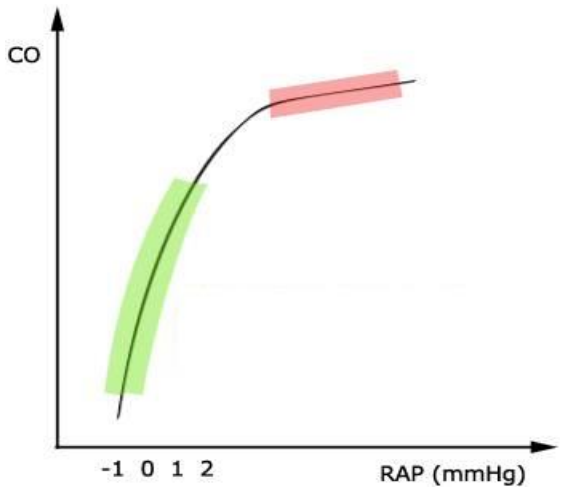

Figure 6: Frank-Starling Law of the Heart. Increased right atrial pressure (increased preload) produces a sharp increase in cardiac output in the physiological range for RAP.

A key point of control is right atrial pressure (RAP). If CO stayed constant, then an increase in MSFP would increase RAP. (Why? Because pressure would increase throughout the circulation, and the greatest percentage increase would be at the right atrium, where pressure was initially lowest.) However, in real life, CO would not stay constant: we know from Starling's experiments (Figure 6 & Figure 7) that the increased RAP (i.e., increased pre-load) will increase stroke volume and hence CO, ensuring RAP stays close to zero.

The effect of changes in afterload is more subtle. Physiologically, afterload may be increased by arteriolar vasoconstriction causing an increase in TPR. From the CO equation above, one might expect increased TPR to decrease CO, but *it does not* due to the Frank-Starling mechanism. Instead, increased afterload, because it results in ventricular stretch, increases the force of cardiac contraction. This allows stroke volume and hence CO to remain constant (Figure 7). Thus increased TPR causes increased ABP, not decreased CO. (This will be covered in more detail in Lecture 6, Control of Arterial Blood Pressure).

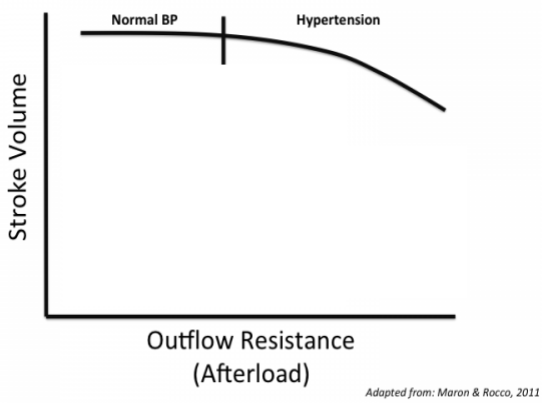

Figure 7: Frank-Starling Law of the Heart. Increased afterload *does not* decrease stroke volume, as might be expected. Instead, force of contraction increases to ensure that CO remains constant with changes in afterload in the physiological range for ABP.

Above (discussion around Figure 2), we saw that MSFP *limits* CO. By considering the Starling mechanism, we can go further: **increased MSFP *causes* increased CO** under normal physiological conditions. Conversely, **decreased MSFP decreases the maximum CO**: this is why blood loss, for

example, decreases blood pressure, and one reason why exercise is impaired by severe dehydration.

What about heart rate? If heart rate changes in isolation, then stroke volume drops and cardiac output barely changes; the heart cannot "pull" more blood from the venous system. However, increased heart rate in exercise, for example, facilitates increased cardiac output by steepening the curve of CO vs. RAP.

Control of MSFP

Mean systemic filling pressure is therefore a critical determinant of cardiac output. **MSFP is determined by the volume of blood and the mean tension in blood vessel walls**.

MSFP can be doubled by increasing the blood volume by 20%, because that doubles the stressed volume. This also doubles the cardiac output. Conversely, because only the "last 20%" of the blood volume actually stretches vessel walls loss of 20% of the circulating volume would be expected to reduce MSFP (and hence CO) to zero.

Fortunately, the mean tension in the blood vessel walls can be regulated. About 60% of blood is in the venules and small veins, and thus **venoconstriction can reduce the capacity of the circulation** such that MSFP can be maintained above zero until about 40% of the circulating volume is lost. This is accomplished by sympathetic venoconstriction, which can up to treble MSFP.

Note that venoconstriction does not significantly influence TPR, which is primarily determined by the resistance of arterioles. Conversely, arteriolar constriction increases TPR but does not influence MSFP, because less than 1% of blood is contained within the arterioles.

Another way to look at things

Rather than consider the entire circulation, it may sometimes be helpful to consider the circulation in two parts: the part in which pressure is above MSFP, and the part in which pressure is below MSFP. We can then consider cardiac output and venous return separately (even though they must be equal):

CO = (ABP – MSFP) / TPR

VR = (MSFP – RAP) / RvR

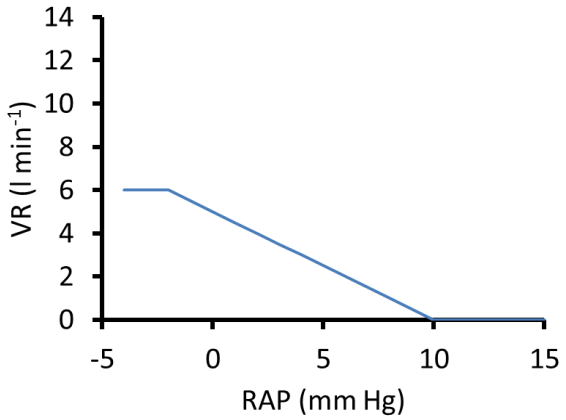

Figure 9: Venous return (VR) is reduced by increased RAP (as VR = (MSFP – RAP)/RvR, and is *zero when RAP = MSFP*. Note also that decreased RAP only enhances VR while RAP is not too negative: for significantly negative values of RAP, venous collapse impedes VR. An increase in MSFP would shift this curve upwards, while a decrease in RvR would make it steeper.

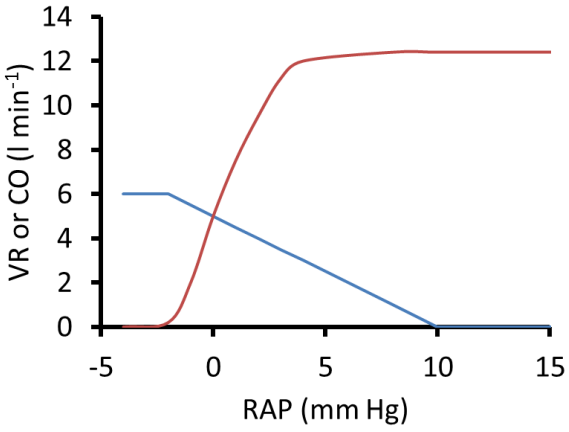

Figure 8: Cardiac output (CO) plotted with the same venous return curve as Figure 9. RAP enhances CO by the Starling mechanism. VR and CO absolutely MUST be equal, as the heart neither creates nor stores blood. The crossing point of these two curves therefore gives the actual values of CO, VR and RAP for given venous return and cardiac output curves.

The only new term here is **RvR, the resistance to venous return**. And it is an oddity. It is perhaps best to think of it as a term that reflects the difficulties blood has in returning to the heart - such as the fact that capillary pressure in the feet is insufficient to drive blood more than a meter upwards to the heart, so that venous return from the lower legs must wait for voluntary muscle movements to

pump blood back. Thus, RvR can *change*, especially in exercise, but it isn't specifically regulated. The venous return equation allows us to consider venous blood flow at different values of RAP (Figure 9).

In isolation, Figure 9 suggests that venous return drops as RAP increases: this is simply because the difference between MSFP and RAP gets smaller. Thus, it also shows the RAP at a venous return of zero, which is of course the mean systemic filling pressure. Raising MSFP by increasing circulating volume or venoconstriction would shift this curve up. Reducing RvR would increase the slope without changing MSFP (i.e. it would not change the intersection of the line with the x-axis).

RAP does not just influence venous return, though. By the Starling mechanism, increased RAP increases cardiac output (Figure 8):

The cardiac output and venous return must be the same, which is where the curves cross (for this system, at an RAP of 0 mmHg and a CO of 5 l min^{-1}). Note that if the RAP was 5 mmHg, CO would transiently exceed venous return, which would cause RAP to drop until VR and CO became equal again.

These curves are helpful because MSFP only shifts the VR curve, and TPR or changes in myocardial contractility only shift the CO curve. Figure 10 shows the effects of sympathetic stimulation as an example.

Figure 10 allows consideration of two effects of sympathetic stimulation *separately*. Without any such stimulation, the system rests at point A (RAP 0 mmHg, CO 5 l min^{-1}). Sympathetic venoconstriction increases MSFP and hence shifts the venous return curve higher at any RAP (as VR = MSFP – RAP). This upward shift means that, for a moment, VR exceeds CO, but as this increases RAP, CO increases and the system settles at point B: raised RAP and raised CO. If, instead, we had *only* increased sympathetic stimulation to the heart, the cardiac output curve would shift to higher outputs at any RAP. However, as this drives RAP negative, the increase in CO is minimal, to point C. Finally, combining the two effect shifts both curves to overlap at point D: a higher cardiac output with RAP remaining at zero.

These "Guyton curves" can be helpful in considering the effect of various changes to the circulation. For example, imagine what would happen with a failing heart, such that CO was reduced at every RAP: the crossing point would slide down the VR curve such that CO would reduce somewhat and RAP would increase significantly.

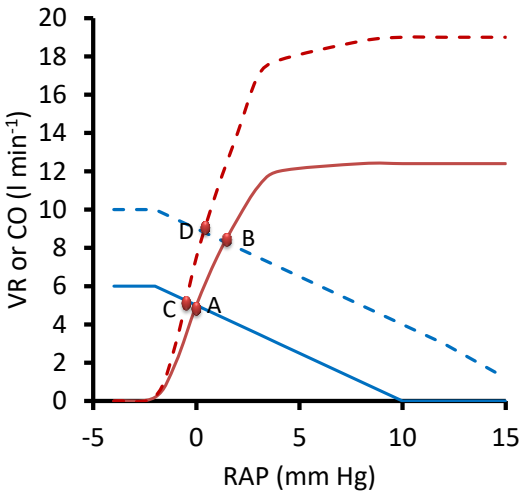

Figure 10: Guyton's curves allow consideration of the effects of sympathetic stimulation on VR and CO separately. Solid lines are without stimulation (as Figure 8), and dashed lines are with sympathetic stimulation. The significance of the labelled points (A-D) is described in the text.

However, these curves are simply a model, or a way of thinking. As discussed above, it is also possible to think about the circulation in terms of a single pressure / flow relationship.

Cardiac output in cardiac disease

What if the heart is *unable* to increase output? Then, an increase in MSFP would increase RAP, but CO could not increase. This has serious consequences: if RAP increases, then capillary pressures must also increase (as blood must still flow from capillaries to veins to the right atrium.) This results in extravasation of fluid and hence oedema.

Unfortunately, the body has no way of knowing that the normal mechanism of increasing cardiac output – increased MSFP – is no longer able to do so. Thus, in heart failure, oedema can be considered to result from the body's attempts to raised cardiac output.

This will be considered in more detail in a later lecture.

Circulatory shock

If the cardiac output is inadequate to supply sufficient metabolic substrates for aerobic respiration to all the tissue, it is a life-threatening medical emergency. The term for this is circulatory shock, or simply **shock**. You will notice already that this term is grossly misused in the media. The typical signs are hypotension and tachycardia accompanying signs of reduced organ perfusion, such as low urine output and loss of consciousness.

It can result from a failure of cardiac output due to a severe loss of circulating volume (**hypovolaemic shock**) see Figure 11. Shock can also be caused by cardiac pathology (**cardiogenic shock**) or due to a severe fall in vascular tone (**distributive shock**), both of which will be covered later in the course.

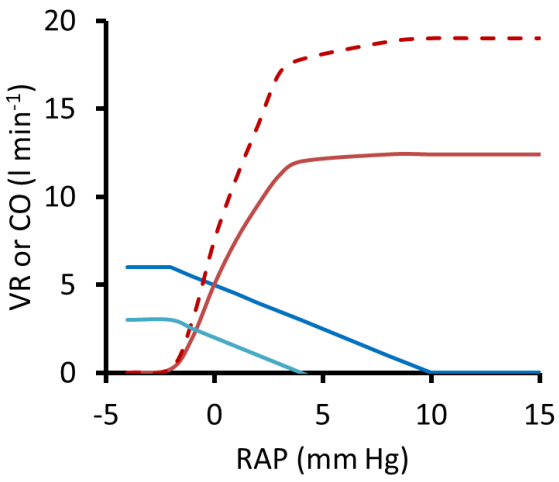

Figure 11 – A severe drop in circulatory volume will lead to hypovolaemic shock, in which the maximum attainable cardiac output is inadequate to perfuse organs. Here, loss of volume reduces MSFP (remember, this is the intercept of the VR curve on the x-axis), and this shifts the VR curve down. No matter what the heart tries to do maximum VR and CO are inadequate. The dotted line might show the effect of sympathetic stimulation on the heart – note that this is unable to increase CO meaningfully without an increase in MSFP.

Lecture 6: The control of arterial blood pressure

The mean arterial blood pressure (ABP) is the *principal variable controlled by the cardiovascular system*. By keeping ABP constant, blood flow to individual tissues can be regulated simply by controlling the local arteriolar resistance, and the circulation thereby approximates a ***constant pressure / variable flow system***. Its principal determinants are Cardiac Output (CO) and Total Peripheral Resistance (TPR). Physiological and pathological processes cause significant changes in TPR and CO; for example, exercise greatly reduces TPR, and blood loss reduces MSFP and hence CO. Thus, control processes are necessary to maintain a relatively constant ABP.

Arterial blood pressure (ABP)

During each cardiac cycle, the heart rapidly ejects blood into the aorta, causing the pressure to rise to a peak called the **systolic blood pressure**, which is normally about 120 mmHg. This creates a pressure gradient towards the rest of the circulation, so blood flows away from the aorta and the aortic pressure reduces to a trough value, the **diastolic blood pressure** of about 80 mmHg, before the next heart beat raises pressures again to systolic values (and this occurs about 2.5 *billion* times in an average lifespan!)

Because of the shape of the pressure wave, the mean blood pressure is approximately the diastolic pressure plus 1/3rd of the pulse pressure. **The pulse pressure is the difference between the systolic and diastolic pressures**.

Mean blood pressure tends to increase with age, and is slightly higher in men than women (between puberty and menopause). The pulse pressure (i.e. the difference between systolic and diastolic pressure) can increase if arterial compliance reduces, such as occurs with atherosclerosis. The pulse pressure also increases if blood can flow away faster in diastole, as occurs physiologically in exercise (where TPR drops), or pathologically if the aortic valve leaks. In situations where the pulse pressure increases, the mean pressure stays constant (i.e. systolic pressure rises as diastolic pressure falls). **This strongly suggests that mean ABP is the principal regulated variable**. How is mean ABP regulated?

Regulation of mean ABP

From Darcy's equation for the whole circulation:

ABP = CO x TPR

This highlights that anything which changes CO or TPR will stress ABP control. It also shows that control of CO or TPR can be used to control ABP. TPR is primarily a function of arteriolar resistance, and from Starling's experiments, afterload (i.e. TPR acting through changes in ABP) does not greatly influence CO. Thus, CO and TPR can be thought of as largely *independent* of each other, providing two separate mechanisms for the regulation of ABP. In order to regulate ABP, though, there must be mechanisms for monitoring ABP.

Broadly, there are three mechanisms for monitoring blood pressure: high pressure baroreceptors; arterial chemoreceptors; and low pressure baroreceptors. Prof. Giussani showed you how the baroreceptors work in Lecture 4 of this series. In this lecture, we will look at how the signals from each are integrated in the CNS to produce the overall regulatory response.

High pressure baroreceptors

As Prof. Giussani discussed, arterial blood pressure can be sensed by mechanoreceptors at strategic high-pressure sites. These are the carotid sinus (just beyond the bifurcation of the carotid artery) and the aortic arch baroreceptors. In addition, the afferent renal arterioles have an important baroreceptor function that will be discussed in the renal physiology lectures. In each case, stretch-sensitive nerve endings are intermeshed within elastic lamellae in regions with relatively little collagen and smooth muscle, such that **stretch triggers increased activity** in baroreceptor fibres of the glossopharyngeal nerve (carotid sinus) and vagus (aortic arch.) These stimulate neurons in the

Nucleus Tractus Solitarius (NTS) in the medulla that **inhibit the vasomotor centre**.

Different baroreceptor fibres have different sensitivities to blood pressure, enabling groups of fibres to cover quite large ranges in blood pressure, from perhaps 50-200 mmHg (the carotid sinus is more sensitive than the aortic arch, whereas the aortic arch can respond at pressure above which the carotid sinus response saturates.)

This was originally discovered in the 1920s: Heymans won a Nobel Prize for showing that increased blood pressure at the carotid sinus produces a reflex reduction in blood pressure. He did this in cross-circulation experiments with two dogs, A and B. The carotid sinus of dog B was connected into the circulation of dog A. Dog A was injected with noradrenaline, increasing its blood pressure, and this triggered an almost immediate reflex fall in blood pressure in dog B.

Denervation of arterial baroreceptors has an interesting effect (see Figure 12): ABP becomes much more variable, but mean ABP stays relatively constant.

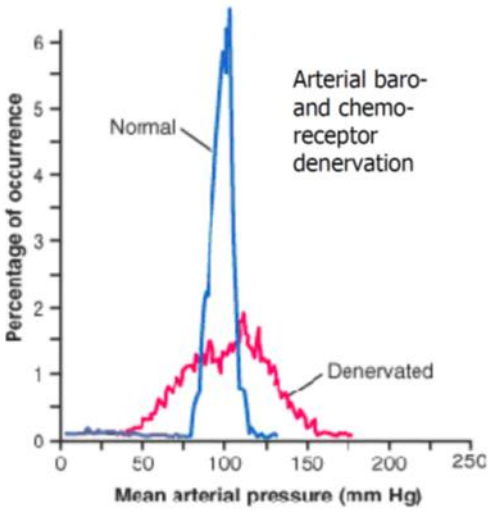

Figure 12: The effect on mean ABP of chronic carotid and aortic baro- and chemoreceptor denervation. Note the profound increase in ABP variability, but little change in the mean ABP.

This increased variability results from such physiological stresses as changes in activity level or changes in posture. This demonstrates the importance of high-pressure baroreceptors and chemoreceptors (see below) in the **short-term control of ABP**. However, the constancy of *mean* ABP suggests that it is regulated by other mechanisms. Indeed, if mean ABP changes, high pressure baroreceptors reset and regulate around the new mean ABP.

Arterial and central chemoreceptors

Chemoreceptors in the carotid and aortic bodies and in the medulla exist primarily to regulate ventilation, as you will learn more about in the respiratory lectures. They are not important in blood pressure control under normal physiological conditions. However, the arterial chemoreceptors do have a role in ABP control when blood pressure is *very* low or when P_{O2} is very significantly reduced. Nevertheless, their responses may then be important because the high pressure baroreceptors are relatively unresponsive under conditions of severe hypotension.

Under such extreme conditions, the carotid and aortic bodies detect low O_2 delivery, and the medullary chemoreceptors detect high arterial CO_2 via the resultant reduction in brain pH. The afferent signals from the carotid and aortic bodies travel by similar pathways to the baroreceptor signals from the carotid sinus and aortic arch, i.e. the glossopharyngeal nerve and vagus nerve respectively.

Low pressure baroreceptors

The lack of influence of high pressure baroreceptors and chemoreceptors on mean blood pressure strongly suggests that longer-term control of ABP involves other detection mechanisms. Due to the importance of MSFP in the determination of ABP, it is perhaps unsurprising that stretch receptors also exist in strategic low-pressure areas of the circulation: the junctions of the atria with their corresponding veins and in the atria themselves. Collectively, these are called the **cardiopulmonary baroreceptors**.

These stretch receptors essentially detect RAP: if RAP is raised, this suggests that the circulation is over-filled such that the heart cannot maintain low venous pressures. This is seen in heart failure and

can lead to oedema as capillary pressures rise. Conversely, **if RAP is low (zero or slightly negative), this suggests that cardiac output is maximal for the current MSFP**.

Denervation of these receptors along with the high pressure baroreceptors produces a rise in mean ABP which is additional to the increased variability seen with high pressure baroreceptor denervation (Figure 13).

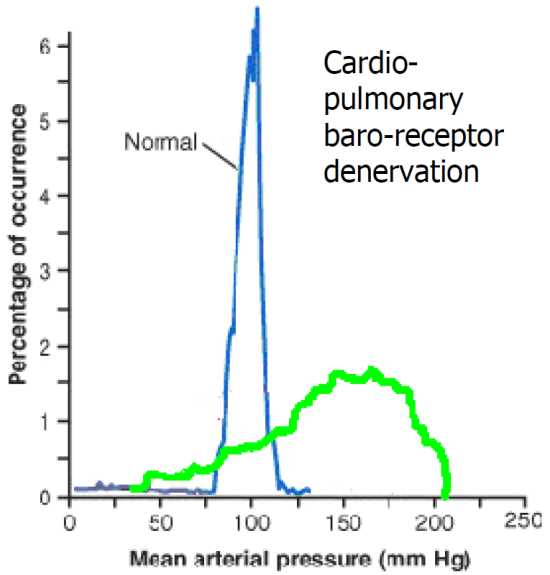

Figure 13: The effect on mean ABP of cardiopulmonary baroreceptor denervation in addition to carotid/aortic denervation. Note a marked increase in mean arterial pressure.

The firing rate of these receptors increases with pressure. The afferent signals travel via the vagus nerve, to the nucleus tractus solitarius (NTS) in the medulla, and thence to the hypothalamus. There, they influence secretion of ADH, sympathetic activity (especially the renal nerves), thirst, and possibly sodium appetite. The net effect is that reduced pressure produces fluid and sodium retention, thereby raising the circulating volume and MSFP. The details of these processes will be covered in the renal physiology lectures next term.

Non-feedback control systems

Baroreceptors and chemoreceptors act within feedback systems, and their importance is clear from denervation experiments. However, common stresses on ABP regulation such as exercise and standing up, and even mild to moderate blood loss, do not cause detectable drops in ABP, and so cannot be entirely reliant on feedback. These common stresses trigger **feed-forward** mechanisms to preserve ABP.

Thus, a drop in ABP can be prevented in exercise by inputs to the medulla from the cortex (where a "decision" to exercise might be taken), from the cerebellum (as part of a co-ordinated motor "programme") and from muscle and joint receptors (as a direct response to movement).

Similarly, pain and emotions such as fear and anger (involving the cortex and hypothalamus), can also provoke a rise in blood pressure: essentially part of the fight-or-flight preparation for dealing with whatever one is worried or frightened of, and perhaps helping the body to deal with any incipient blood loss.

Integration of baroreceptor and "feed-forward" signals in the medulla

Before this starts to look dauntingly complex, there is some good news. The feed-forward mechanisms feed into the same area of the brain – the cardiovascular centre of the medulla – as the baro- and chemoreceptors. A summary of the main neural pathways for all these systems are summarised below Figure 14.

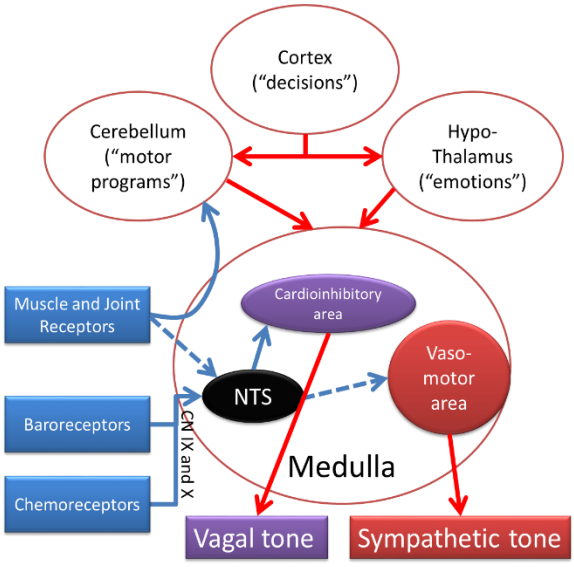

Figure 14: Nuclei within the medulla oblongata integrate baroreceptor and chemoreceptor signals (from cranial nerves IX and X to the NTS – nucleus tractus solitarius) with "feed-

forward" inputs from muscle/joint receptors and higher brain areas. The final common effector pathways are sympathetic nerves to the heart and circulation (via the Bulbospinal pathway) and parasympathetic innervation of the heart.

The effector pathways

The medulla then generates a response, informed by sensory input from the circulation as well as more "strategic" inputs from higher brain centres. This enables it to control ABP via two major efferent pathways: the sympathetic and parasympathetic divisions of the autonomic nervous system. Sympathetic outflows act on the vasculature and the heart, and the parasympathetic outflow is solely to the heart. However, it is worth noting that *other* autonomic pathways that will not be discussed here are involved in the control of *local* blood flow for specific processes, such as in sweating, salivation and digestion.

Sympathetic efferents

Bulbospinal pathways (i.e. from the medulla to the spinal cord) activate pre-ganglionic pathways, primarily at glutamatergic synapses between levels T1 and L3 of the spinal cord. These pre-ganglionic neurons synapse at nicotinic synapses with postganglionic sympathetic neurons found within prevertebral and paravertebral sympathetic ganglia. The postganglionic sympathetic nerves involved in ABP control run with the large blood vessels to innervate muscular arteries, arterioles and veins. Increased sympathetic activity generally causes *vasoconstriction* (including venoconstriction) through the action of noradrenaline on α_1 adrenoceptors.

Arteriolar vasoconstriction increases TPR, while venoconstriction increases MSFP. Sympathetic activity also causes some redistribution of blood flow, as the vasculature of some organs receives little significant sympathetic vasoconstrictor innervation: in particular, arteries and arterioles supplying the brain and the heart show little if any vasoconstriction during cardiovascular reflex responses.

Sympathetic vasoconstrictor nerves are tonically active, with a resting action potential frequency of 1-4 Hz. Their activity can increase to around 10 Hz which can reduce blood flow to some tissues to almost zero *in extremis*, such as in catastrophic haemorrhage. The resting tone allows inhibition of sympathetic activity (e.g. from the baroreceptor reflex) to reduce ABP. It also means, for example, that spinal cord damage above T1 causes a severe and rapid drop in blood pressure by abolishing this resting sympathetic outflow.

Sympathetic fibres also supply the heart (cardiac accelerator nerves), innervating the SA node, atria and ventricles. They increase both heart rate and contractility, and have a low resting frequency.

Finally, some preganglionic sympathetic fibres in the splanchnic nerves innervate the chromaffin cells of the adrenal medulla. Their activity stimulates adrenaline release into the circulation, which acts on the heart and vasculature in a broadly similar manner to direct sympathetic innervation, via α_1 receptors. However, some tissues – notably coronary blood vessels and skeletal muscle – have more β_2 than α_1 receptors. β_2 receptors trigger vasodilatation, thereby increasing coronary and skeletal muscle blood flow. However, note that noradrenaline from sympathetic nerves primarily acts on α_1 receptors, which allows skeletal muscle blood flow to be limited if necessary.

Parasympathetic afferents

The vagus nerve innervates the SA node, AV node and the cardiac conducting system. Its activity slows the heart rate and slows conduction through the heart, lengthening the cardiac cycle. It does not influence force. The vagal supply to the heart is one of the rare parasympathetic pathways that shows tonic activity. Inhibition of the vagus at rest, using atropine, produces significant acceleration of the heart rate.

Integration and effectiveness of circulatory control

There are many challenges to blood pressure regulation in everyday life. Activities as diverse as running, digestion, sweating and even thinking require increased blood flow to specific organs or systems that necessitate local vasodilatation (the next three lectures will cover how this vasodilatation comes about). The resultant fall in

TPR can be very large: as much as five or six-fold in whole-body intensive exercise. Yet, mean ABP stays relatively constant (Figure 15).

Since ABP = CO x TPR, any fall in TPR would be expected to produce a fall in ABP unless there was an adequate response. Small adjustments can be effected by sympathetic vasoconstriction of blood vessels, and indeed some tissues such as skeletal muscle, skin and the gastrointestinal tract receive more blood that is required to meet their metabolic demands at rest. However, any significant fall in TPR demands an increase in CO. This ultimately requires sympathetic venoconstriction to increase MSFP, in concert with reduced vagal and increased sympathetic stimulation of the heart, to increase heart rate and contractility (ensuring raised MSFP produces a rise in CO without necessitating an increased RAP). Together, these manoeuvres increase CO and hence maintain mean ABP.

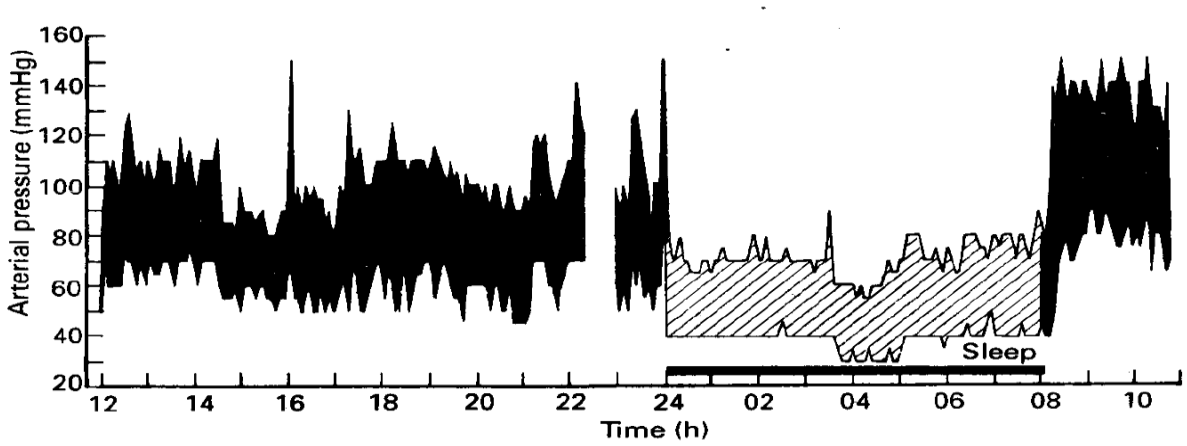

Figure 15: Arterial blood pressure recorded from a normal human over a 24 hour period. Mean ABP remains relatively stable, though drops during sleep and shows two sharp rises at 16:00 and 24:00, accounted for by a painful stimulus and sexual intercourse, respectively.

It is important to note that this lecture concerns the **short-term control of blood pressure**. Over longer periods, **the circulating volume is a critical determinant of MSFP** and hence ABP. You will learn about its control in the renal physiology lectures.

Hypertension

So far, we have been thinking primarily about how the body maintains an *adequate* blood pressure to ensure adequacy of the circulation. However, in clinical practice we are often more concerned with high blood pressure, or **hypertension** than with low blood pressure.

What is hypertension, and why is it a problem? Hypertension is defined as an arterial blood pressure (ABP) greater than 140/90 mmHg in humans. It is a clinical problem because it leads to overwork of the heart, and damage to blood vessels. Together, these problems may then lead to cardiac failure, cardiac arrhythmia and ischaemic damage to organs, such as myocardial infarction or stroke.

Perhaps the first thing to make clear is that hypertension *does not cause normal blood vessels to burst*! Normal blood vessels can withstand enormous pressures: systolic pressures of up to 400 mmHg have been recorded in weightlifters during lifts.

However, it is true that *abnormal* blood vessels might rupture under pressure; atherosclerosis both causes arterial wall damage, and is caused by hypertension.

Atherosclerosis is the build-up of inflammatory lipid deposits beneath the endothelium of blood vessels. These grow in thickness and progress in structure to include fibrous and calcific layers. They can produce problems by:

1) Narrowing blood vessels thereby restricting flow.

2) Endothelial damage, promoting clotting (thrombosis)
   a. Local blockage
   b. Distant blockage (embolism)
3) Weakening blood vessel walls, leading to aneurysm (and rarely to rupture).

Hypertension accelerates the development of atherosclerosis and is one of the most important risk factors (alongside diabetes, smoking and obesity). It seems likely that the mechanism by which raised ABP leads to atherosclerosis is by damage to the endothelium, though the precise mechanism of this is unclear.

Hypertension: cardiac effects

Atherosclerosis affects the coronary arteries, which supply the heart with blood. This can result in cardiac ischaemia: this is felt as pain, termed angina pectoris, and also limits the amount of work the heart can do.

Cardiac ischaemia is a particular problem in hypertension because the heart has to pump blood *into* the arteries. Thus, raised arterial pressure increases the work demanded from the heart. The normal response of muscle to increased workload is *hypertrophy* – that is, enlargement of the cells of the heart and hence an increase in cardiac mass.

Exercise induces "eccentric hypertrophy" in which the ventricular volume increases along with the muscle mass (the heart grows). In contrast, hypertension induces "concentric hypertrophy" in which the heart muscle expands *inwards*, thereby reducing the ventricular volume. This produces three major problems:

1) Increased myocardial oxygen demand.
2) *Diastolic dysfunction*, in which cardiac filling and hence stroke volume is impaired.
3) Increased risk of cardiac arrhythmias (see below).

In addition, if blood pressure remains high and especially if the cardiac blood supply is poor, concentric hypertrophy can progress to ventricular dilatation in which in addition to filling poorly, the heart is also unable to fully empty – *systolic dysfunction.*

Lecture 7: Control of capillary blood flow

ABP is maintained at a relatively constant level by central mechanisms. As flow = pressure gradient / resistance, this constant pressure gradient allows blood flow through individual tissues – even individual capillary beds – to be regulated simply by regulating the upstream (arteriolar) resistance. There are three principal mechanisms for the regulation of arteriolar resistance: nerves; hormones and other vasoactive substances; and local tissue metabolism. Arteriolar resistance reflects a balance of these often opposing influences, as, for example, local demand for vasodilatation competes with systemic signals regulating ABP. This lecture first looks at why capillary flow and pressure is regulated, and then at how this regulation is achieved in general. The next lecture looks in more detail at the influence of flow and pressure in capillaries.

Capillary blood flow and arteriolar resistance

Blood flow through tissues must be regulated to ensure adequate local delivery of O_2 and metabolic substrates, and removal of CO_2, lactic acid etc. Indeed, blood flow is so well matched to metabolic demand that over the whole body, cardiac output is usually proportional to $\dot{V}_{O2}$, the volume of O_2 used per minute. Indeed, $\dot{V}_{O2}$ is often measured as a proxy for CO in studies of athletes, for example.

Flow is always a function of the pressure gradient and the resistance. The flow through a capillary bed downstream from a single arteriole is therefore given by:

$$\dot{Q} = \frac{P_a - P_v}{R_{pre} + R_{cap} + R_{post}}$$

Where the pressure gradient is the difference between P_a (the arterial pressure) and P_v (the venous pressure), and the resistance is the sum of the series resistances of the pre-capillary, capillary and post-capillary resistances. However, because the arteriolar resistance makes up about 70% of this total series resistance and is the only directly regulated resistance, and because the pressure gradient is usually kept fairly constant, we can simplify the relationship to:

$$\dot{Q} \propto \frac{1}{R_a}$$

In general, **local control of arteriolar resistance (R_a)** matches local blood flow to local metabolic demand, whilst **central, autonomic control of arteriolar resistance** controls TPR to maintain a constant mean ABP. This means that it is entirely possible for local demand to produce vasodilatory signals that are in opposition to generalised vasoconstrictory signals. Local control can be metabolic, myogenic, or from vasoactive compounds released in a paracrine fashion by the capillary endothelium. Central control is neurogenic or endocrine.

Arteriolar smooth muscle is arranged circumferentially (Figure 16). Thus, its contraction increases the tension in the vessel wall and hence causes vasoconstriction. Relaxation of the smooth muscle reduces vessel wall tension, allowing the blood pressure to open the vessel, causing vasodilatation. The tension in vascular smooth muscle is primarily a function of the intracellular Ca^{2+} concentration, but can also be modulated by phosphorylation of myosin light chain kinase.

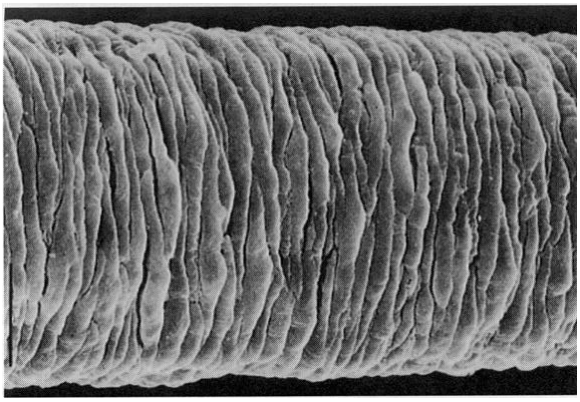

Figure 16: Arteriolar smooth muscle, showing the circumferential arrangement of fibres. Arteriole diameter ~60 µm.

Control of arteriolar smooth muscle

There are multiple systems that regulate arteriolar tone and probably many redundancies, such that blocking any of several systems individually will have little effect, whereas blocking them all reveals that each nevertheless has an influence. For this

reason and others, control of vascular tone is not fully understood.

However, the control pathways all converge on two broad intracellular control systems that are better understood: regulation of the myosin-binding site of actin by caldesmon (Figure 18a), and regulation of myosin light chain by phosphorylation (Figure 18b).

Metabolic control of arteriolar resistance

It is very simple to demonstrate local regulation of blood flow. Blood flow can be measured in the arm, and then a cuff is inflated around the upper arm to above arterial pressure for around ten minutes. When the cuff is remove, a profound increase in blood flow through the arm will be recorded. This is termed reactive or **functional hyperaemia**.

Understanding the mechanism of functional hyperaemia is considerably more complicated than demonstrating it.

The best-studied vasculature is probably that of skeletal muscle, where rapid and enormous changes in metabolic rate occur under physiological conditions and are reproducible in experiments. Its control will be considered in more detail in the final lecture on the circulation in exercise. Nevertheless, in all tissues, changes that typically accompany increased metabolism, or normal metabolism in the face of reduced local blood flow, include reduced P_{O2}, increased P_{CO2}, decreased pH, increased adenosine and increased extracellular K^+. These factors promote vasodilatation of systemic arterioles (though note that reduced P_{O2} and increased P_{CO2} have the opposite effect in the pulmonary circulation, where such changes reflects poor ventilation and not poor perfusion.)

In addition, changes that accompany anaerobic metabolism, including decreased pH and increased lactic acid concentration, also stimulate vasodilatation. This appears to be a direct effect of intracellular pH on smooth muscle.

Myogenic control of arteriolar resistance

If blood vessels behaved as rigid tubes, flow through them would be proportional to the

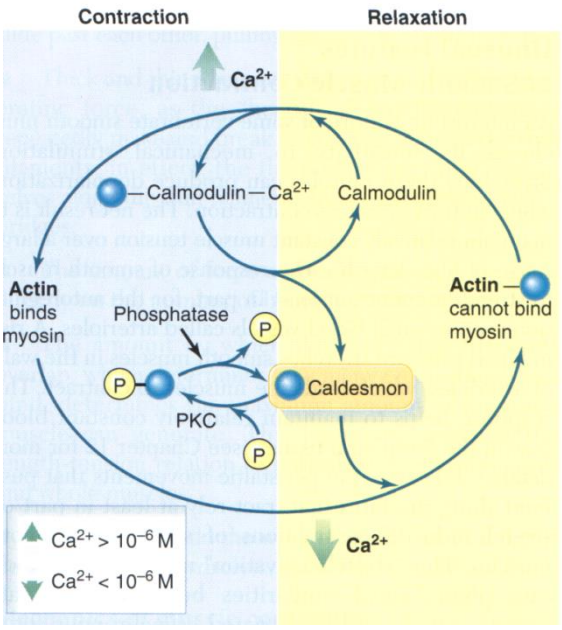

Figure 18a: Regulation of the myosin-binding site of the actin filaments. Caldesmon (depicted as a sphere) binds to actin, blocking myosin-actin interaction, unless bound to Ca^{2+}-calmodulin or phosphorylated by protein kinase C (PKC).

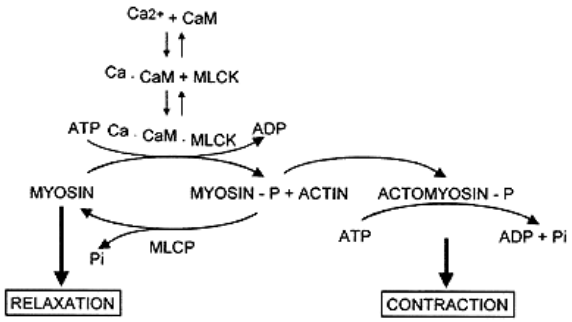

Figure 18b: Regulation of the myosin light chain (MLC). Myosin light chain kinase (MLCK), when activated by Ca^2-calmodulin, phosphorylates MLC. This promotes its binding to actin. If dephosphorylated when bound to actin, latch bridge formation can occur (not shown here).

pressure gradient. However, if pressure changes then some vascular beds – particularly those of the brain, heart and kidney – respond by changing their diameter to reduce the change in flow. Thus, increased pressure leads to increased resistance, and flow increases much less than would be expected. This also serves to maintain a constant capillary pressure in these organs; this may reflect the poor lymphatic drainage of heart and brain, and

the necessity of regulating filtration pressures in the kidneys.

Note that myogenic autoregulation will tend to have a similar effect to metabolic autoregulation. Thus, increased arterial pressure would tend to *directly* cause vasoconstriction by the myogenic mechanism, and *indirectly* cause vasoconstriction as increased perfusion washed out local metabolites.

The role of the endothelium

The capillary endothelium is in the optimal physical location to detect local changes in metabolism. Its importance in regulating vascular responses was first noted when it was realised that acetylcholine could dilate arteries only when the endothelium was intact (whereas noradrenaline constricted them even when the endothelium had been removed); see Figure 19.

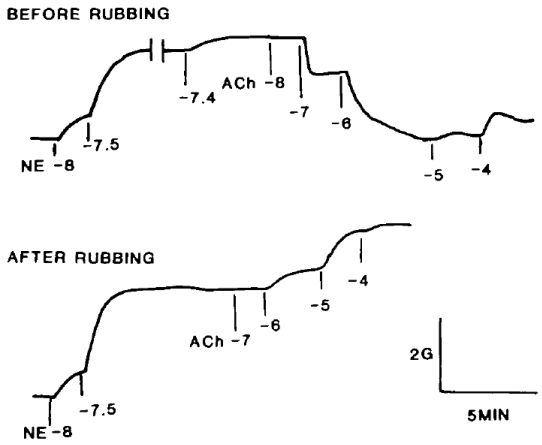

Figure 19: Robert Furchgott's experiments showing the influence of noradrenaline (NE – norepinephrine) and acetylcholine (ACh) on the tension in pre-contracted rabbit aorta before and after the endothelium was removed by rubbing with a wooden stick. The numbers denote the logarithmic concentration of each drug and 2g denotes 2 grams of tension. Tension normally decreases with ACh (vasodilatation) and increases with noradrenaline (vasoconstriction), but the ACh effect requires an intact endothelium.

Furchgott, Ignaro and Murad won the Nobel Prize in 1998 for the discovery that the signal from the endothelium to the vascular smooth muscle was NO (nitric oxide.) Thus, acetylcholine (and a vasodilator peptide, bradykinin) stimulate NO production by the action of nitric oxide synthase on L-arginine in the endothelium. NO is lipophilic and diffuses quickly, stimulating a soluble guanylyl cyclase in the vascular smooth muscle. A cGMP-dependent protein kinase then phosphorylates MLCK, inhibiting it.

Vasodilator drugs based on nitrates have been used for over 130 years, ever since it was realised that nitroglycerin relieved angina (and caused severe headaches.) More recently, sildenafil (perhaps better known as Viagra) was discovered to reduce cGMP breakdown, thus enhancing this pathway, (by inhibiting cGMP-specific phosphodiesterase type 5).

More generally, endothelium releases a range of vasodilator and vasoconstrictor substance, as well as pro-coagulants, anti-coagulants, fibrinolytics, antibacterials, growth factors etc. Under physiological conditions, the net effects of this are anticoagulant and vasodilatory. Thus, **endothelial damage** or dysfunction is associated with raised vascular resistance, hypertension, atherosclerosis and an increased risk of clots. Such endothelial dysfunction may result from diabetes, hypertension, smoking, atherosclerosis, hyperlipidaemias etc., and so may represent an important common pathway for the circulatory pathology associated with these risk factors.

Systemic control of arteriolar resistance

In the previous lecture, we saw how the medulla can regulate TPR via sympathetic noradrenergic innervation of arterioles. This acts via the α_1 receptor: this is linked to the G-protein $G\alpha_q$, which activates phospholipase C, raises IP_3, and thereby triggers Ca^{2+} release from the SR.

Circulating adrenaline can also act on α_1 receptors, but in addition causes vasodilatation of the coronary arterioles and skeletal muscle through β_2 receptors. These are linked to the G-protein $G\alpha_s$, which activates adenylate cyclase, raising cAMP levels and thereby activating protein kinase A (PKA). PKA phosphorylates myosin light chain kinase

(MLCK), reducing its activity and hence reducing the phosphorylation of myosin light chain (MLC).

Finally, and beyond the scope of this lecture, blood flow can be controlled in specific organs for a variety of reasons. A particularly well-studied example is control of skeletal muscle flow during the initiation of exercise. This will be discussed in the final lecture. In addition, examples including thermoregulatory increases in skin blood flow, increased gastrointestinal blood flow during digestion, and in particular the control of renal arterioles, will all be discussed in your other lecture series.

Other vasoactive substances – eicosanoids

Eicosanoids are arachidonic acid derivatives with actions on blood vessels (amongst others). They are involved in clotting and inflammatory responses. Most are synthesised by the enzyme cyclo-oxygenase, and are therefore of some clinical significance because this is the enzyme that is inhibited by **aspirin** (COX-1) and certain other non-steroidal anti-inflammatory drugs.

The eicosanoids include a number of substances called **prostaglandins**, which can be vasoconstrictory (PG-F) or vasodilatory (PGs I, D and E). They are involved in the inflammatory response, and in some of the changes that take place during parturition.

Another eicosanoid, **thromboxane A_2** is produced by platelets and is a very potent vasoconstrictor, and also causes platelet aggregation. It is an important part of the clotting response. Its actions are opposed by another eicosanoid, **prostacyclin** (PG I_2) produced by the endothelium. Endothelial damage tends to alter the balance between these two substances in favour of thromboxane A_2, and hence can lead to reduced blood flow and clotting. This is the rationale behind using aspirin to prevent myocardial infarction: aspirin irreversibly blocks COX-1, required to produce both these substances, but because endothelial cells have nuclei but platelets don't, endothelium can synthesise more COX-1, and hence produce prostacyclin, whereas the production of thromboxane A_2 is significantly diminished.

Lecture 8: Capillary flow and pressure

The whole purpose of the circulation is to deliver blood to the tissues, and the capillaries are the exchange area between the circulation and the tissues. Exchange of substances between cells and capillaries is primarily by diffusion, so no cell can be far from a capillary. Water movements across the capillary membrane are also a function of hydrostatic pressures, and have important influence on the volume of the circulation and the interstitial compartments. As exchange occurs between capillaries and their surrounding tissue, the composition of blood plasma and interstitial fluid becomes more similar, and thus exchange slows. Increased flow of blood into the capillaries opposes this dissipation of gradients by delivering fresh plasma from the arterial circulation, and thus accelerates exchange.

Capillaries

Capillaries are extremely numerous: for example, skeletal muscle contains about 500,000 capillaries per gram, and it has been calculated that the total surface area of capillaries is about 5000m^2! However, only about 20-25% of capillaries are perfused at rest; the rest are empty and collapsed, but can open as the tissue becomes more active.

Capillaries consist of a single layer of endothelial cells, connected together by interendothelial junctions, and surrounded by a basement membrane. The endothelial cells themselves are permeable to gases (O_2 and CO_2). Most capillaries are also permeable to water and crystalloids (ions): water can pass through cells *via* aquaporins (AQP1) and between cells, whereas crystalloids can generally *only* diffuse between cells. Finally, most capillaries are normally relatively impermeable to colloids, such as plasma proteins, though protein permeability can increase in inflammation.

However, the structure of capillaries varies in different organs, giving profound regional differences in capillary permeabilities to different substances. This should not be a surprise given the different requirements of different organs. For example, capillaries in the lung primarily need to exchange O_2 and CO_2, whereas in the liver, they must also allow passage of newly synthesised plasma proteins, while in the renal glomeruli, bulk flow of water is required.

Capillaries fall into three groups according to their "leakiness":

1) Continuous capillaries. This is the most common type, and generally has interendothelial junctions about 10-15 nm wide that allow relatively free passage of water and ions, except in the brain and the testes where there are narrow tight junctions between cells.
2) Fenestrated capillaries. These are often found in epithelia such as the small intestine and glands. Fenestrae ("windows") through the cells allow ion diffusion through as well as between cells.
3) Sinusoidal (discontinuous) capillaries. These are found e.g. in the liver. Large gaps between cells as well as fenestrae allow transendothelial passage of proteins.

Capillary exchange of solutes

According to Fick's law, the mass flow $\dot{Q}$ (in mol s^{-1}) of a solute, X, between the capillary (c) and the interstitial fluid (if) across the capillary membrane depends on its **permeability (*P*), the surface area (*A*) and the concentration gradient ($[X]_c - [X]_{if}$):**

$$\dot{Q}_X = A_c P_X ([X]_c - [X]_{if})$$

This equation is useful in considering how the delivery of a solute to a tissue might be changed in response to a change in that tissue's requirements. Examining the terms of the equation in turn:

A_c (capillary surface area). As most capillaries are not perfused at rest, increasing the number of capillaries that are perfused in a tissue will increase the area for exchange, and will reduce the mean diffusion distance.

P_X (the permeability of substance X). Endothelial cells can change shape in response to signalling molecules such as cytokines, widening interendothelial clefts. An example is the increased

leakiness of capillaries in response to histamine as part of the inflammatory response.

$[X]_c$ (the capillary concentration of X). This primarily depends on two factors: the rate of delivery of X into the capillary (capillary blood flow x arterial concentration) and the rate of extraction of X from the capillary (i.e. $\dot{Q}_X$ itself).

$[X]_{if}$ (the interstitial fluid concentration of X). This also depends on two factors: the rate at which X is "used up" in the local tissue, and the rate at which it is extracted from the capillary.

Thus, if the O_2 usage of a tissue increases this will tend to reduce $[O_2]_{if}$ and, by increasing the concentration gradient, increase $\dot{Q}_{O2}$ (i.e. increase the uptake of O_2 from the capillary). However, this would tend to reduce $[O_2]_c$: fortunately, $[O_2]_c$ can be maintained by increasing blood flow (i.e. increasing the delivery of arterial blood, high in O_2, to compensate for the increased removal of O_2 from the capillary).

Capillary exchange of water

Water movements across the capillary wall are important because they influence both the circulating volume and the local interstitial fluid volume. Yet, water behaves rather differently from the generic solutes considered above. As first outline by Starling in 1896, water movements across the capillary wall are *convective* rather than purely diffusive, as is the case for solutes. The driving force for water movements across the capillary wall are the **hydrostatic pressure difference (ΔP)** and the ***effective* osmotic pressure difference ($\Delta\pi$)**:

ΔP is the difference between the hydrostatic pressures in the capillary (P_c) and in the interstitial fluid (P_{if}). P_c drops along the length of the capillary as a result of resistance and some outward movement of water. P_{if} can be *negative* in non-encapsulated organs with respect to atmospheric pressure – perhaps -1 to -2 mmHg. The interstitial "fluid" is a complex gel of proteoglycans and water within a network of collagen fibres. Due in particular to water removal by the lymphatics, the matrix is slightly under-filled such that its elastic recoil provides an expanding force, much as sucking water out of a sponge leaves it ready to suck water back in. In capsulated organs, such as muscle, the brain and the kidney, P_{if} tends to be slightly positive.

$\Delta\pi$ is the *effective* osmotic pressure, also called the colloid osmotic pressure or the oncotic pressure difference. Only solute that *cannot easily cross* the capillary wall can exert an osmotic force, so the osmolarity of Na^+, K^+ etc. is not relevant to $\Delta\pi$. Instead, it is determined by the osmolarity of the solute that *cannot* cross the capillary, i.e. the plasma protein (the colloid). These include albumin, globulins and fibrinogen, and their total concentration is very small, approximately 1.5 mM. Nevertheless, because the colloid content of the interstitium is very low, the resultant osmotic gradient is of comparable magnitude to the hydrostatic pressure gradient.

Starling's equation, similar to the Fick equation, is simply that volume flow (J_V, in ml cm^{-2} s^{-1}) is equal to the hydraulic permeability (**K**, in ml min^{-1} $mmHg^{-1}$ cm^{-2}) multiplied by the net filtration pressure (ΔP - $\Delta\pi$):

$$J_V = K((P_c - P_{if}) - \sigma(\pi_c - \pi_{if}))$$

Note that the terms of $\Delta\pi$ are multiplied by **σ, the colloid reflection coefficient**. This is a dimensionless correction factor between 0 and 1, to account for any leakiness of the capillary to proteins. At 1, this implies total impermeability to protein such that the full colloid osmotic pressure is expressed, and if less than one it implies that the membrane is slightly leaky to proteins and so they cannot exert their full osmotic effect.

The net filtration pressure (ΔP - $\Delta\pi$) changes significantly along the length of a capillary, primarily due to the fall in ΔP, as shown in Figure 20. This usually results in water movement *out of* the early parts of a capillary and *into* the late parts. The slight remaining pulsatility of the blood pressure also causes a temporal variation in filtration rate.

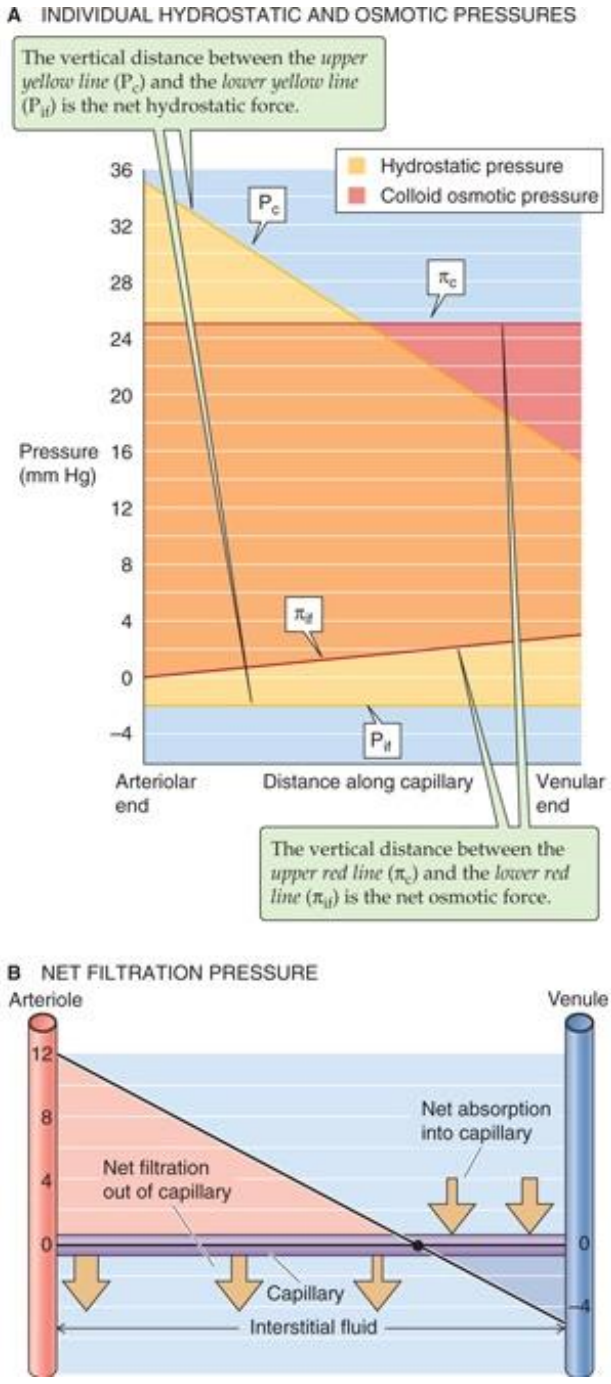

Figure 20: Component pressures (A) and net filtration pressure (B) in a typical systemic capillary. From Boron & Boulpaep, Medical Physiology 2e, 2012, Saunders.

The significance of Starling filtration-reabsorption

The **balance** between hydrostatic and colloid osmotic pressures varies throughout the body and at different times. For example, pressure at the venous end of the capillary is raised in the feet when standing. These forces are also influenced by arterial blood pressure, venous pressure, resistance in the upstream arteriole, colloid pressure and the leakiness of capillaries to proteins. We will consider some of these factors in more detail in the renal physiology lectures.

In terms of understanding the circulatory influence on Starling forces, it is important to realise that **capillary pressure (P_c) closely follows venous pressure**, but is not closely related to arterial pressure. This is because P_c must always be higher than venous pressure. Thus, P_c will inevitably rise with venous pressures in, for example, heart failure. In contrast, because of the high-resistance arterioles between arteries and capillaries, and because of metabolic autoregulation of arteriolar diameter, **high ABP is not usually associated with increased capillary blood flow, nor increased P_c.**

However, *reduced* ABP may indeed result in *reduced* P_c – in part as a direct result, and in part because of increased sympathetic drive and arteriolar vasoconstriction. This is actually very helpful after blood loss as it allows **tissue fluid to buffer blood volume** in a process called **autotransfusion**. This is why the haematocrit (i.e. the *concentration* of red blood cells) falls after blood loss: tissue fluid dilutes the blood. This fall in haematocrit is a more sensitive marker of blood loss than is a fall in blood pressure.

The lymphatic system

It is important to note that in most capillaries at most times, there is a small net outward movement of water from the capillaries. This clearly doesn't result in continual swelling of our tissues, so where does it go? The answer is: into the lymphatic system.

Lymphatics begin as small thin-walled channels of endothelium in the interstitium that join to form progressively larger vessels until they ultimately allow fluid to return, via the thoracic duct, into the vascular system at the subclavian veins. The initial lymphatics have multiple interendothelial junctions between cells that behave like micro-valves, allowing fluid in, but preventing its egress. These empty into larger collecting lymphatics that, like small veins, have valves and some smooth muscle in the walls.

Each day, a net 2-4 litres of fluid leaves the capillaries by Starling filtration, and is returned to the circulation by the lymphatics. The lymphatics also return some 100-200 g of protein each day. The importance of this mechanism is seen in **lymphoedema**, which results when the lymphatic drainage to a limb, for example, is blocked (this can occur due to infections such as filiariasis or due to tumour, for example.) It is important to note that the lymphatic system also has an important role in the immune system that is beyond the scope of these lectures.

Oedema

If the rate of filtration of fluid out of capillaries exceeds its removal by the lymphatics, fluid will collect in the interstitium, expanding the extracellular space. This is called interstitial oedema. It can be localised or more generalised (though even in generalised oedema the effects of gravity on venous pressure tend to make the swelling greatest in the lower parts of the body.)

Oedema increases the distance between cells and capillaries and therefore interferes with solute exchange. In the systemic circulation, this can starve cells of nutrients. In the pulmonary circulation, fluid can collect in the alveoli, interfering with gas exchange and decreasing lung compliance.

Localised oedema can result from lymphatic blockage or from increased capillary leakiness to proteins in inflammation, ischaemia-reperfusion injury, and in the brain following head injury.

Generalised oedema is only noticeable when the interstitial fluid volume has increased by about 30%, or 3 l. This is equal to the plasma volume, so must develop relatively slowly and requires salt and water retention by the kidneys. It can be caused by loss of colloid proteins in malnutrition, or from the kidneys in the nephrotic syndrome. However, the most common cause in the developed world is congestive cardiac failure. Due to its importance, this will be discussed in a little more detail.

Congestive cardiac failure

To understand heart failure, it is important to understand what exactly the heart is failing to do. In severe, end-stage heart failure, there is a failure to adequately perfuse organs, resulting in organ failure and eventual death if untreated. In less severe heart failure, it is necessary to think more carefully about the heart's precise role.

On the most basic level, the heart's role is to pump blood from the veins to the arteries, so heart *failure* implies that atrial pressure is too high, and arterial pressure is too low. Then, it is necessary to understand what constitutes "too high" atrial pressure, and "too low" ABP. Too high atrial pressure is straightforward: atrial pressure should be close to zero, because if it is any higher it impedes venous return and tends to raise capillary pressures. A non-failing heart, by the Starling mechanism, and assisted by sympathetic stimulation in e.g. exercise, maintains RAP close to zero.

What is "too low" ABP? This is slightly more complicated, because it is quite possible – indeed, very common – to find symptoms of heart failure and hypertension in the same patient. This is because heart failure develops when ABP is *lower than the set point* and cannot be raised. The body responds to this broadly as it does to haemorrhage (see lecture 9 and the renal physiology lectures): increased sympathetic drive causes venoconstriction, arteriolar vasoconstriction, and (with renal responses) retention of fluid. Together, these raise TPR and MSFP. Normally, TPR does not influence CO (Starling mechanism) but this may not be true in a failing heart because maintaining CO with increased TPR requires an increase in cardiac work. Similarly, CO is normally limited by MSFP (i.e. it is as high as it can be without raising MSFP). In heart failure, CO is instead limited by the heart, so raising MSFP will not produce a significant increase in CO, but will instead cause atrial pressure to rise. This is summarised in Figure 21.

The symptoms of heart failure primarily result from 1) an inability to adequately increase CO; and 2) the increased atrial pressure. An inability to adequately increase CO reduces exercise capacity and may

induce feelings of fatigue (see lecture 9). Raised atrial pressure implies raised venous pressures and hence raised capillary pressures. This causes oedema: peripheral oedema in right-sided heart failure and pulmonary oedema in left-sided heart failure.

Understanding the physiology of heart failure is key to understanding its treatment. Often, there is little that can be done to improve cardiac output (though valve repair, pacing, coronary bypass etc. can be used to treat failure resulting from valve disease, rhythm disorders and severe angina respectively). However, drugs that inhibit the *responses* to low blood pressure, such as angiotensin converting enzyme (ACE) inhibitors, diuretics, and beta adrenergic blockers, can produce significant symptomatic relief, by lowering MSFP and TPR. Can you see how this might both reduce oedema, and reduce cardiac oxygen demand, perhaps even without decreasing CO?

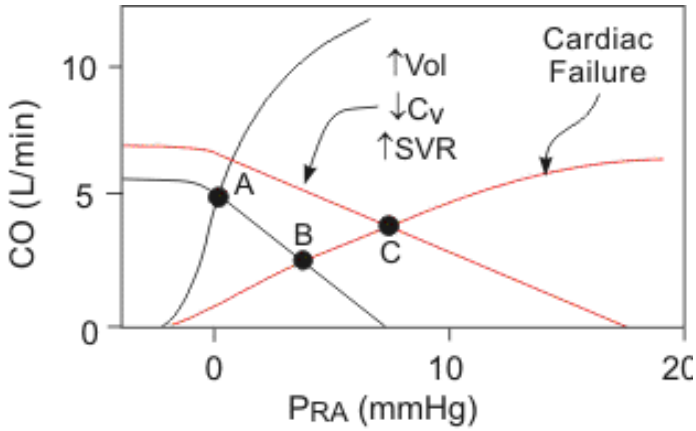

Figure 21: Venous return and CO curves for a normal heart (crossing at point A) and a failing heart. Point B shows the effect of a failing heart *without* an increase in MSFP: note that CO is very low and RAP is raised. A compensatory increase in blood volume and venoconstriction shift the venous return curve upwards (higher at any RAP), but the resultant increase in CO (to point C) is minimal. Instead, RAP is raised, which is likely to lead to raised capillary pressures and oedema.

Lecture 9: Exercise and haemorrhage: the cardiovascular responses to specific stresses.

This lecture considers the physiological responses to some relatively common stresses. This will revise some of the control systems covered in the earlier lectures and consider how they produce an integrated, coordinated response. It will also allow some insight into the limiting factors in exercise.

The cardiovascular response to exercise

Exercise can be one of the greatest physiological stresses to homeostasis, particularly in competitive sports when activity levels are maximised, and in cardiovascular disorders where the potential responses are limited. The increased metabolic demand of muscles during exercise requires increased blood flow (functional hyperaemia) that is primarily regulated by local mechanisms.

In individual muscles, blood flow can increase from resting levels of 2-3 ml^{-1} min^{-1} $100g^{-1}$ of muscle to 35 ml^{-1} min^{-1} $100g^{-1}$, a ~17-fold increase, suggesting a 17-fold decrease in local resistance at constant ABP. However, skeletal muscle makes up ~40% of body mass, so dynamic exercise involving multiple muscles will profoundly influence TPR. In intense exercise, TPR may drop to ~20% of its resting value; without cardiovascular homeostatic mechanisms, this would produce a catastrophic drop in ABP to 20% of its resting value!

Systemic mechanisms are responsible for maintaining ABP and cardiovascular homeostasis despite this drop in TPR. The systemic responses can result in a ~5-fold increase in cardiac output (~3-fold increase in heart rate and ~50% increase in stroke volume). They may also partially oppose the locally-mediated vasodilatation in muscle, such that the increase in blood flow through muscles exercised in isolation can exceed the flow through the same muscle during whole-body exercises.

Functional hyperaemia

Blood flow to active muscles increases very rapidly during exercise. The response has two distinct phases: Phase I, in which blood flow increases very rapidly from ~2 to 15-20 s after the initiation of contractions; and Phase II, from about 20 s after initiation of contractions, during which there is a slow increase in blood flow to sustained high levels (Figure 22).

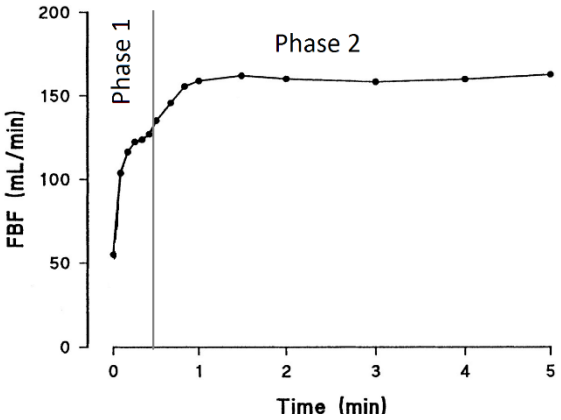

Figure 22: forearm blood flow (FBF) during hand-grip exercises. FBF increases rapidly between ~2 and 20 s (Phase I), then increases more slowly to a sustained high level (Phase II).

As mentioned in Lecture 7, activity in muscle, like in any tissue, results in a wide range of local changes that influence arteriolar diameter, including reduced P_{O2}, increased P_{CO2}, decreased pH, increased extracellular K^+, lactic acid production, as well as increased extracellular ADP, AMP and adenosine. Are any of these of particular importance?

The fast phase of exercise hyperaemia

It is *relatively* straightforward to identify the most important factors in the initial, rapid Phase I increase in blood flow. This is because most local changes occur too slowly to explain this rapid phase of the increase in blood flow. The first exception is K^+: muscle action potentials produce immediate and fast increases in extracellular [K^+] to as much as 10 mM, depending on activity levels, within 5-10 s (Figure 23).

The rise in interstitial [K^+] has a very unexpected effect: it *hyperpolarises* arteriolar smooth muscle, which closes voltage-gated Ca^{2+} channels and thereby relaxes the muscle (see Figure 18). This is odd: one would expect raised extracellular [K^+] to cause depolarisation. The mechanism of the

observed hyperpolarisation seems to be a combination of two effects: raised extracellular [K^+] both enhances Na^+/K^+-ATPase activity, and also enhances the activation of inwardly-rectifying K^+ channels (K_{IR}). The increased intracellular K^+ and increased K^+ permeability together result in hyperpolarization. Pharmacologic blockade of either the Na^+/K^+-ATPase or K_{IR} (using ouabain or barium respectively) attenuates vasodilatation by approximately 60%.

The second fast cause of functional hyperaemia is the "muscle pump" whereby muscle contractions accelerate venous return. As discussed below, this enhances CO, but may also reduce local venous pressures, thereby enhancing the pressure gradient through muscle capillaries.

In some animals, but probably not in humans, neurogenic vasodilatation also plays a role. In the cat, for example, sympathetic *cholinergic* nerves directly cause a rapid increase in blood flow to muscle at the start of exercise. Circulating adrenaline can also cause vasodilatation of muscle: this is not fast enough to contribute to phase I, but may be released as part of an *anticipatory response*.

The maintained phase of exercise hyperaemia

It has been difficult to precisely identify the mechanisms of Phase II hyperaemia. Multiple redundancies mean that when the release or action of one substance is inhibited, the magnitude of hyperaemia can change little because other factors then make a larger contribution. Furthermore, changes in some key concentrations profoundly influence others: for example, reduced P_{O2} clearly alters skeletal muscle metabolism and the resultant metabolic products, making it difficult to separate direct responses to P_{O2} from responses to its downstream influences. Nevertheless, it is possible to identify some components of the response.

Raised extracellular K^+ continues to have an important role. Activation of β_2 receptors on vascular smooth muscle by circulating adrenaline has a vasodilatory effect.

A direct effect of reduced P_{O2} on muscle arterioles is unlikely, because although P_{O2} falls in muscle capillaries during exercise, it has not been shown to fall in the vicinity of the arterioles. However, increased offloading of O_2 from haemoglobin results in the release of ATP and NO from red blood cells. Low O_2 also enhances the activity of the ectonucleotideases that produce vasodilatory adenosine from ATP. Adenosine also accumulates around active muscle fibres: the source may be ATP released by active muscle and acted on by extracellular ectonucleotideases. This release of ATP is at least partly via CFTR channels in response to reduced intracellular pH, thereby linking pH changes to the vasodilatation.

Adenosine is a strong vasodilator, acting on A_{2A} receptors to increase cAMP levels in smooth muscle. This activates protein kinase A (PKA), which in turn opens K_{ATP} channels. This hyperpolarises the cell by the same mechanism as K^+ accumulation, and may therefore act synergistically with increased K^+.

Lactic acid has not been shown to have a direct effect that is distinct from its effect on pH.

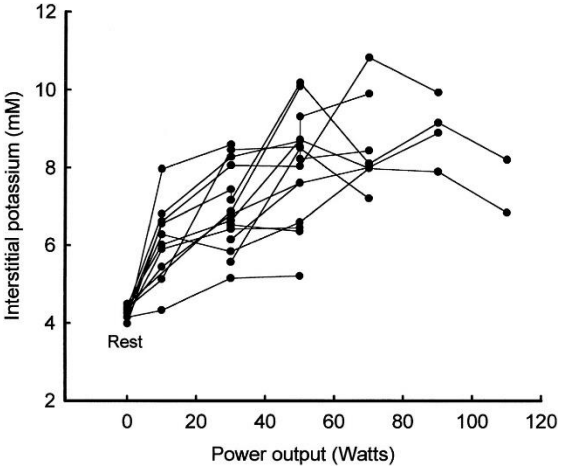

Figure 23: human knee-extension exercises, showing interstitial [K^+] around the active quadriceps muscle fibres rises markedly during activity, and can easily double at moderate exercise intensity. Note that the trace showing the least rise in [K^+] was from a subject unable to perform the higher-intensity exercises. What might this suggest?

A summary of functional hyperaemia

Functional hyperaemia in exercise is complex and incompletely understood. Nevertheless, its *effects* are clear: exercising muscle receives a blood supply that is closely matched to its metabolic demands.

Furthermore, this increase in blood flow results largely or wholly from *local* vasodilatory influences. It is then left to systemic control processes to prevent the resultant reduction in TPR from having dire consequences.

Systemic circulatory control in exercise: dealing with the consequences of functional hyperaemia.

Exercise produces a drop in TPR, to as little as 20% of its resting value in intense exercise. This necessitates an increase in CO in order to maintain ABP. As we saw in previous lectures, this is achieved by sympathetic venoconstriction (to increase MSFP), reduced cardiac vagal stimulation (to increase HR) and increase cardiac sympathetic stimulation (to increase HR and myocardial contractility).

In addition, the "muscle pump" action of contracting muscles on nearby veins pushes blood towards the heart due to the presence of venous valves. This can be considered to reduce the resistance to venous return, thereby increasing VR at any given MSFP. Thus, MSFP may increase 3-fold in exercise, yet VR and CO might increase 6-fold, suggesting that activity of the "muscle pump" approximately halves RvR. The net result of these influences actually causes mean ABP to *rise* slightly in exercise (see Figure 26, below).

What produces the increased sympathetic activity and reduced cardiac vagal activity? As shown in Figure 14, the cardiovascular centre in the medulla is well positioned to coordinate a response to circulatory changes in exercise: it receives inputs from higher brain centres involved in "deciding" to exercise, from muscle and joint sensors that respond to movements, and from arterial baro- and chemoreceptors. Which are most important?

It is possible to separate the central command to exercise from the actual occurrence of exercise using curare to block the neuromuscular junction (Figure 24). This clearly demonstrates that the increase in heart rate during exercise can occur *without* any actual exercise occurring. Such centrally-mediated cardiovascular responses correlate with the perceived effort of exercise.

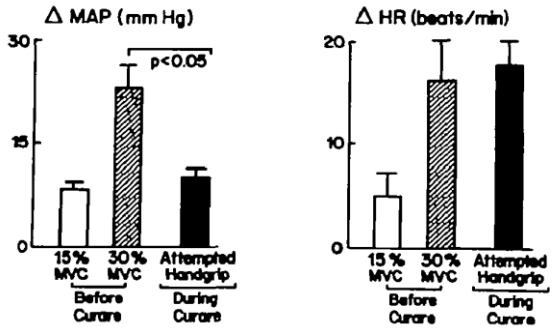

Figure 24: measurement of mean arterial pressure (MAP) and heart rate (HR) during a static hand grip exercise at a force equal to 15% and 30% of maximum voluntary contraction (MVC), and during an attempt to perform the same hand grip with muscles paralysed by curare. Despite the lack of muscle activity, central command still produces an increased HR in the presence of curare, although little increase in MAP.

Indeed, it is possible to record increased heart rate even before exercise begins (Figure 25).

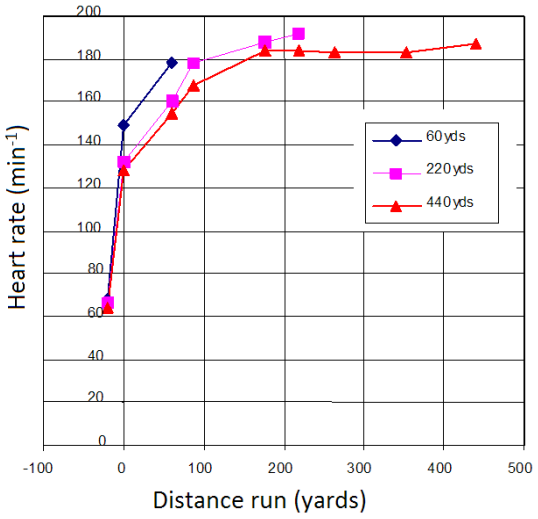

Figure 25: Heart rates before and during a sprint of different durations. Note that heart rates at a distance of zero (i.e. *before* starting to run) are approximately double the resting values (plotted at a negative distance).

What, then, is the role of the baroreceptors in exercise? Their influence appears, by an unknown but centrally-commanded mechanism, to reset, possibly in part due to joint and position sensors competing with the baroreceptor inputs to the nucleus tractus solitarius. The effective result is that the baroreceptors then maintain the stability of

blood pressure around a slightly raised set point Figure 26.

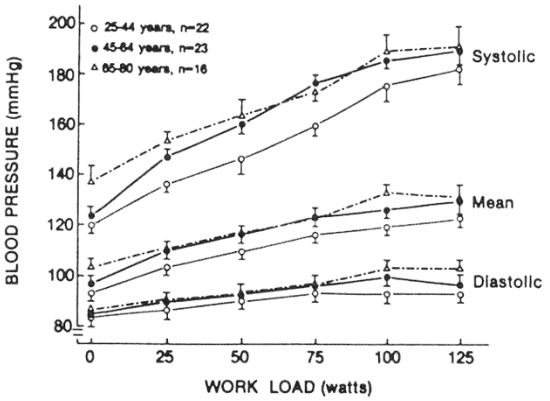

Figure 26: blood pressures during exercise of different intensities. Note that mean blood pressure rises slightly, strongly arguing that feedback control of ABP does not play a primary role in the circulatory response to exercise. Note too that the pulse pressure widens (systolic blood pressure rises more than diastolic) reflecting increased myocardial contractility and decreased TPR.

Limiting factors in exercise

The highest cardiac outputs are seen in exercise. Thus, it is reasonable to ask if cardiac output might *limit maximum performance*, or whether maximum performance is limited by some other factor, such as the ability of muscles to perform work, or the rate of O_2 uptake in the lungs. The answer depends on a person's level of fitness, but is relatively easy to ascertain.

With normal lungs, O_2 uptake is not limiting, as can be shown by measuring performance at normal and raised levels of P_{O2}: raising inhaled P_{O2} does not significantly improve performance.

In reasonably fit people, it can be shown that the ability of muscles to perform work is not limiting by comparing power output when pedalling an exercise bike with one leg versus pedalling it with two. Power output with two legs is *less than double* power output when using just one leg. This suggests that during two-legged cycling, muscles are not able to produce their maximum power output. Note, however, that less fit people may not have sufficient muscle aerobic capacity to sustain high enough power outputs to produce this effect, and may instead be limited by their unfit muscles.

Together, this suggests that the circulation provides the ultimate limitation on whole-body power output during exercise. Note that this limitation exists despite mean blood pressure being sustained even in the most intensive exercise. To put it another way, it is not possible to exercise so hard that ABP drops, suggesting that there is central regulation of activity levels according to circulatory requirements. To put it another way, one component of the feeling of fatigue must relate, albeit indirectly, to circulatory capacity.

Exercise in disease states

The ability of relative circulatory inadequacy to regulate activity levels and produce the feeling of fatigue has important consequences in disease states involving reduced maximum cardiac output. This particularly includes heart failure, for which fatigue may be a prominent feature.

Haemorrhage

The response to haemorrhage usually comprises a response to two stimuli: reduced blood volume, and pain / emotional state.

Uncompensated loss of blood causes, sequentially, a reduction in blood volume, MSFP, venous return / cardiac output, and hence blood pressure. Arterial baroreceptors (carotid sinus and aortic arch) and low-pressure baroreceptors (terminal great veins and atria) detect these changes, reducing inhibition of the medullary vasomotor areas. Higher brain centres (cortex and hypothalamus) may also stimulate these areas as a response to pain or fear.

This produces rapid (within seconds) responses. Sympathetic nerves increase arteriolar and venous tone and the heart rate, and vagal tone to the heart decreases. In addition, catecholamines, angiotensin II and ADH are released. These all have vasoconstrictory effects, especially in high concentrations, but also have important effects on fluid balance that will be covered in the renal physiology lectures.

Within minutes, two changes in the microvasculature also contribute. The first is reverse stress relaxation, whereby smooth muscle

contracts when stretch is reduced. The second is mobilisation of tissue fluid as reduced capillary pressures shift the balance of Starling filtration-reabsorption forces towards reabsorption of fluid. This can contribute perhaps 500 ml – 1 l to the circulating volume.

In the longer term (onset in tens of minutes), renal conservation of water and salt, thirst and sodium appetite act to restore the circulating volume.

Finally (24-48 hours) plasma proteins are replaced by synthesis in the liver, and (to 5-7 days) increased red blood cell production restores lost erythrocytes. This is stimulated by the release of erythropoietin from the kidneys in response to reduced oxygen delivery.

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