11. Cardiovascular System

11.1 Introduction

The cardiovascular system (CVS) provides the mechanism by which the *blood* contained within it is *circulated* through the tissues of the body. It is composed of a *cardiac pump* and a series of distributing and collecting *vascular tubes* linked by very thin *capillaries.* The structure of these capillaries permits rapid *diffusion* of substances over the short distance between the blood and the interstitial fluid bathing the cells of the tissue. Thus the CVS is a *transport system* and, in the last analysis, it links the external environment to the tissues and distributes substances essential for metabolism. These are O_2 from the lungs and nutrients from the GIT. At the same time, the CVS removes from the tissues CO_2 and other by-products of metabolism, carrying them to the lung, kidney and liver. Such actions of the CVS are essential for *homeostasis* of the plasma component of blood and the intersitial fluid, which both comprise the ECF or internal environment, and hence ensure the even distribution of available water and electrolytes to all parts of the body.

It also circulates the hormones of the endocrine system. It is concerned with the distribution of heat and maintenance of body temperature which requires the control of blood flow to heat-exchanging areas. It also transports the substances involved in blood coagulation and the cells and antibodies concerned with defence mechanism.

Basic Design and Functions of the Components of the CVS

The heart consists basically of two pumps lying side by side but functioning in series: the right-hand one receives blood from the body and then propels it at low pressure through the lungs (the *pulmonary circulation*); the left-hand one receives blood from the lungs and then propels it at high pressure to all other tissues of the body (the *systemic circulation*). There is in adults normally no direct communication of blood between the two pumps. Thus in one cycle, all the blood has to circulate through the lungs but only a small portion circulates through any one systemic tissue since these are arranged in parallel.

Blood flow distribution is related to the weight of the tissue, to its level of activity and, in the case of the kidney and skin, to the extra blood flow required for filtering excretory products and for temperature regulation respectively. During moderate exercise, for example, the total blood flow increases and its distribution changes. Heart muscle and skeletal muscle require increased blood flow to satisfy their increased metabolism and the skin has a higher blood flow to dissipate the extra heat production. Some of this blood is shunted away from the gut and kidney but it is imperative that a constant blood flow to the brain be maintained. Thesee flow changes are controlled by local mechanisms acting on particular blood vessels (arterioles) within the tissue and by some hormones and the autonomic nervous system acting on both the heart and these blood vessels.

The distributing vessel leaving the right-hand side of the heart is the pulmonary artery and leaving the left is the systemic aorta. To supply a tissue or organ, these branch into smaller arteries and finally arterioles before entering the vast capillary network of fine tubes. The capillary network is drained by venules which collect into veins and finally into the pulmonary veins or into the large superior and inferior venae cavae. The heart and each of these vessel types have special roles to play in the CVS.

The *heart* fills with blood during its relaxation phase (*diastole*) and then generates pressure through muscular contraction to expel some of that blood (*systole*). Thus the pumps generate pulsatile pressure, approx. 25 mmHg on the right and approx. 120 mmHg on the left. The frequency of pumping (*heart rate*), the volume ejected at each stroke (*stroke volume*) and the product of these (*cardiac output*) can be altered by some hormones, by the autonomic nervous system and by the mechanism inherent in the heart.

The high pressure conduits of the systemic circulation, the *aorta* and *arteries,* have elastic fibres in their walls which stretch, storing energy as the vessel distends with the stroke volume ejected during systole. During diastole, elastic recoil of the walls releases energy and thus maintains blood flow towards the periphery. Backward propulsion into the heart is prevented by the valve guarding the entrance to the aorta and this prevents aortic pressure falling to zero. In this way intermittent flow from the heart is converted into continuous pulsatile flow through the arteries.

Arterioles have a narrower lumen than arteries and are the major site of resistance to blood flow. The amount of blood flow is inversely proportional to the resistance which is determined mainly by the radius of the tube. The high resistance of the arterioles is reflected in the considerable fall in blood pressure as blood flows through them. This is accompanied by a large damping of the pulsatile flow and its conversion to a steady continuous flow. Arteriolar resistance can be increased, and hence blood flow through to the capillary network decreased, by contraction of circular smooth muscle in the wall of the arterioles and vice versa. Contraction of this smooth muscle is controlled by local mechanisms, by some hormones and by the autonomic nervous system. Such arteriolar constriction will inevitably elevate the pressure in the arteries and decrease the pressure in the capillaries. The adjustment of arteriolar calibre regulates tissue blood flow, aids in the control of arterial blood pressure and alters capillary pressure and hence the net flow of water across the capillary wall.

Capillary networks provide a very large cross-sectional area through which blood flows slowly, giving ideal conditions for diffusional exchange between blood and interstitial fluid. Across the capillary wall lymph plasma is formed from the imbalance between osmosis and ultrafiltration of water. The lymph is returned slowly to the CVS by a secondary set of collecting tubes called the *lymhatic system.*

The primary set of collecting tubules, the *venules* and *veins,* are low pressure conduits returning blood from the capillaries to the heart. Systemic veins have a relatively large capacity. Indeed, veins hold four times as much blood as does the

arterial side in the resting supine position. They are also very distensible and accomodate about 90% of any blood transfusion. Contraction of smooth muscle in the walls of veins, which is controlled by the autonomic nervous system and some hormones, causes a reduction in venous compliance (distensibility) and hence in venous volume (capacity). This shifts proportionally more blood into skeletal muscle capillaries during exercise or into the arteries during the maintenance of arterial blood pressure after a haemorrhage.

At certain sites in the wall of the systemic aorta and carotid arteries, there are nerve endings known as *baroreceptors* which respond to stretch and hence monitor the arterial blood pressure. This information, together with other sensory inputs, is relayed to the *cardiovascular centres* (the coordinating centres in the brain). The resulting motor output alters the *autonomic nervous activity* to the heart, arterioles and veins in order to maintain arterial blood pressure at a certain level whilst altering total blood flow and its distribution.

11.2 The Heart

Functional Anatomy

Providing the AV valves are open, blood will flow onwards into the respective ventricles. When the ventricles are about 80% full of blood, the atria contract almost simultaneously to propel their enclosed blood into the ventricles to complete ventricular filling. After a very short pause, both ventricles contract almost simultaneously and the resulting increase in pressure immediately closes the AV valves. At rest the period of ventricular filling is about two-thirds of the total cycle.

The magnitude of pressure generated by each heart chamber during contraction is reflected in the thickness of its muscle wall. The inner surface of the myocardium is lined with *endocardium* which is a continuation of the endothelium of blood vessels.

Right and lef *coronary arteries* supply the arterioles and capillaries of the myocardium. Venous drainage is via the *coronary sinus (75%)* and *anterior cardiac vein (20%)* which both empty into the right atrium. Some venous blood drains directly via *Thebesian veins* and small venules into all heart chambers. Venous blood entering the left side of the heart in this manner will cause a small reduction in the oxygen concentration of sysemic blood. Blood flow through ventricular myocardium is reduced (right ventricle) or abolished (left ventricle) during the contraction phase of the ventricles because the high pressures generated by the ventricles compress the coronary blood vessels.

Origin and Conduction of Electrical Activity

Although the heart is completely divided internally into right and left chambers, the cardiac muscle fibres of the myocardium of the two atria are continuous as are those of two ventricles. However atrial and ventricular muscular fibres are separated by rings of fibrous tissue called the *atrioventricular ring.* This acts

not only as a fibrous skeleton for the origin and insertion of atrial and ventricular muscle and attachment of heart valves but also as an electrical insultaor separating atria from ventricles.

Cardiac muscle cells are shorter than skeletal muscle cells, are branched and abut end to end to form a network and are rich in mitochodnira. They have one nucleus situated in the centre of the cell. Just as in skeletal muscle, actin and myosin filaments are found in each cardiac myofibril arranged into sarcometers with their characteristic A, I and H bands and M and Z lines. The transverse tubular system is located, however, at the Z line in cardiac muscle not at the A-I junction. The apposition of one cardiac cell with another coincides with one of these Z lines and becomes specialized into a dense *intercalated disc*. Within this disc, areas of plasma membranes of adjoining cells fuse to form *gap junctions* which provide low resistance pathways for the rapid conduction of electrical current between the two cells. This ensures that when an action potential is generated in any part of the cardiac network, it is propagated rapidly so that the atria or ventricles contract as one. The discs also provide a site of adhesion of one cardiac cell with another and ensure that the tension developed by one cell is transmitted through to the next.

A denervated heart continus to beat in an orderly sequence of atrial then ventricular contraction followed by a passive filling phase. This ability to depolarize and contract rhythmically without innervation is called *myogenic rhythmicity*. All parts of the heart have this ability and the inherent rate in the atria and ventricles is about 70 and 40 beats per min respectively. However, the initiation of each beat and its sequential coordination is brought about normally by a *specialized conduction system* of cardiac cells that have few myofibrils and can only contract weakly. Action potentials originate at a rate of about 100 per min in a small area called the *sinoatrial (SA) node* (the pacemaker) located in the right atrium near the entrance of the superior vena cava. From there they are conducted along the plasma membrane from one atrial cell to another through the low electrical resistance of the intercalated discs. Conduction velocity is enhanced by three conducting pathways (anterior, middle and posterior *internodal bands*) causing both atria to contract almost simultaneously. The internodal bands merge as they approach the next node, the *atrioventricular (AV) node*, which is located in the atrioventricular fibrous ring on the right side of the atrial septum. The AV node is the only electrical pathway from atria to ventricles through the insulating fibrous ring. Conduction through the AV node is slow (0.05 m/sec) compated with atrial or ventricular muscle (0.5 m/sec). This effectively delays transmission for about 0.1 sec during resting heart rates and ensures atrial contraction is finished before ventricular contraction begins. From the AV node, action potentials travel at a speed of 1 m/sec in the Purkinje fibres of the *bundle of His* along the right and left branches down the ventricular septum to enter the *Purkinje network* which ramifies throughout the ventricles. The conduction velocity through the Purkinje network is very fast (5 m/sec). Because of the extensive branching of the Purkinje network in the ventricles, excitation reaches all parts of both ventricles rapidly causing both to contract alomst simultaneously.

Characteristics of Cardiac Potentials

The resting membrane potential and the action potential have different characteristics in different regions of the heart. Basically, three patterns are found - one for Purkinje fibres and ventricular muscle, one for atrial muscle and one for the SA and AV nodes. Note that the duration of the action potential varies in different regions of the heart. It is shortest in the SA and AV nodes and atrial muscle, longest in the Purkinje fibres and intermediate in duration in the bundle of His and ventricular muscle.

In ventricular muscle the resting membrane potential is stable at about -90 mV due to the stability of the conductance to K+ and to Na+. The action potential has an initial rapid depolarization (phase 1) resulting from a sudden increase in conductance for Na+ and decrease in conductance for K+ with the *net result* that more Na+ ions enter the cell than K+ ions leave. The peak of the action potential reaches about +20 mV and then has a rapid but short decline (phase 2) leading to a prolonged shoulder or plateau (phase 3). Phase 2 is mainly due to a rapid reduction in conductance for Na+. Phase 3 is due to a slower reduction in conductance for Na+ and a delayed increase in conductance to Ca2+ causing Ca ions to enter the cell. The action potential then repolarizes relatively slowly (phase 4) as conductance for Ca and Na return to normal.

These events contrast with those in axons or skeletal muscle in which conductance for Ca is not involved in the action potential and conductance for K does not decrease during the initial depolarization. The involvement of conductance for Ca in cardiac muscle is responsible for the long duration of the cardiac action potential (about 250 msec) compared with only a few milliseconds in skeletal muscle or axons.

In atrial muscle the action potential has a less obvious plateau (phase 3) and therefore a longer repolarization phase (phase 4) than ventricular muscle due to conductance for Ca decreasing more rapidly in these two phases.

In the SA and AV nodes the resting membrane potential is unstable and slowly depolarizes from about - 70 mV to about - 50 mV in between action potentials. This slow depolarization is called the prepotential or *pacemaker potential.* The instability is due to a slow decline in conductance for K+ without any change in conductance for Na+ or Ca++. When conductance for K+ is sufficiently low, the threshold potential of - 50 mV is reached and this triggers the action potential. It has a relatively slow depolarization (phase 1) due to a slower increase in conductance for Na+ than in ventricular muscle. The peak of the action potential is about 0 mV, there is no plateau and hence the repolarization (phase 4) is long.

The rate of depolarization of the pacemaker potential in the SA node is faster than in the AV node. Therefore the SA node triggers its action potential first and is the pacemaker from which each heart beat originates. The action potential propagates from the SA node through the atria, causing the atrial action potential, and arrives at the AV node before the pacemaker in the AV node has reached its threshold. Thus the action potential that occurs in the AV node is caused by the SA node. The action

potential then propagates through the ventricle causing the ventricular action potential.

Cardiac Refractory Period and the Temporal Relationship Between Electrical and Mechanical Events

During the *absolute refractory period (ARP)*(about 200 msec) of the action potential the cardiac cell is inexcitable and during the subsequent *relative refractory period (RRP)*(about 50 msec) there is a gradual recovery of excitability. A second action potential cannot be generated during the ARP whereas a strong stimulus can elicit an action potential in the RRP. The strength required decreases progressively during the RRP. An action potential generated during the RRP has a slower rate of depolarization, a lower amplitude and shorter duration than usual. Immediately after the RRP, the next action potential is still of a shorter duration and results in less Ca++ entry.

When measured from the beginning of the action potential there is a latency of about 10 msec (compared with about 2 msec in skeletal muscle) befores the muscle starts to contract. The peak of the developed tension occurs just before the end of the ARP and the muscle is half-way through its relaxation phase by the end of the RRP. The total duration of the mechanical event is about 300 msec. Thus the electrical and mechanical events in cardiac muscle overlap considerably in time in contrast with skeletal muscle where the short duration action potential is virtually over before the contraction begins. This overlap means that when a second action potential is triggered at the very end of the ARP or during the RRP, the second contraction is superimposed on the semi-relaxed phase of the first contraction. It is a relatively weak contraction because the shorter duration of the second action potential has resulted into less Ca++ entry into the cell than usual. This means that the force developed by the crossbridges between the actin and myosin filaments will be reduced.

Thus it is impossible to produce the summation and tetanus found in skeletal muscle during high frequency stimulation. The physiological importance of the prolonged cardiac refractory period is that it protects the ventricles from too rapid a re-excitation which would impair their ability to relax long enough to refill adequately with blood. Furthermore, since the total refractory period is longer than the time taken for conduction through the atria or ventricles, recycling of excitation in the muscular network is not seen in the normal heart.

Efferent Regulation of Heart Rate

The *cardiovascular centres* in the brain influence, via sympathetic and parasympathetic nerve fibres and hormones, the basic rate of the heart. Without these nerves the human heart at rest would beat at about 100/min, the normal discharge rate of the SA node. With only the *sympathetic nerve* fibres to the heart active, this basic rate is *accelerated* to about 110/min and with only the *parasympathetic* nerve fibres active the rate is slowed to about 60/min. The normal resting heart rate is about 70 beats/min when modified by both nerves. Thus there is more tonic

discharge from the parasympathetic slowing the heart than from the sympathetic accelerating the heart. Since the parasympathetic nerve fibres travel to heart in the X cranial nerve (the vagus), the parasympathetic effect on heart rate is often referred to as *vagal tone.*

Increased heart rate (*tachycardia*), for example during exercise, results from an increase in sympathetic discharge with a reciprocal decrease in parasympathetic discharge. In moderate exercise the parasympathetic discharge will be silenced. Decreased heart rate (*bradycardia*), for example during sleep or in athletes at rest, results from an increase in parasympathetic discharge with a reciprocal decrease in or even absence of sympathetic discharge. The effect of the autonomic nervous system on heart rate is referred to as *chronotropy* (positive or negative).

The autonomic nervous system alters heart rate by its action on the SA node. *Noradrenaline,* the transmitter released by the postganglionic sympathetic fibres, and *adrenaline,* the hormone released from the adrenal medulla in response to increased sympathetic activity, bind to beta1 adrenergic receptors on plasma membranes of cardiac cells in the SA node. This decreases the permeability of the membrane to K+ and results in an increase in the rate at which conductance for K declines in between action potentials, thereby increasing the rate of depolarization of the pacemaker potential. The threshold pattern is reached earlier and hence the action potential is triggered earlier allowing more action potentials to occur per unit time. *Acetylcholine,* the transmitter released by the parasympathetic fibres, acts on *muscarinic cholinergic receptors* in the SA node causing a decrease in the rate at which conductance for K declines and hence prolongs the pacemaker potential. The rate at which acetylcholine is released and degraded is very quick, so that heart rate can be altered from beat to beat by the vagus in contrast to the slower release and degradation of the sympathetic transmitter, noradrenaline.

Other parts of the heart also receive sympathetic and parasympathetic fibres. The delay at the AV node is reduced by the sympathetic and prolonged by the parasympathetic since, via their effects on conductance for K, they increase and decrease respectively the slope of phase 1 of the action potential in the AV node. The duration of the atrial action potential is shortened by the sympathetic and lengthened by the parasympathetic. The Purkinje fibres and ventricular muscle receive mainly sympathetic innervation, the stimulation of which shortens the duration of their action potentials. Such alterations in the action potential duration are unique to cardiac muscle and shortening and lengthening are caused by a more rapid or a slower decrease respectively in conductance for Ca in phase 3 of the action potential.

The minimum duration of the caridac action potential is about 120 msec in atrial muscle. Thus the theoretical maximum atrial rate of contraction is about 400/min. However, the AV node cannot conduct more than about 220 action potentials per min, so that a coordinated heart cannot beat any faster than about 220 beats per min.

Cardiac Arrhythmias

Arrhythmias are disturbance of the rhythm or sequence of depolarization due to disorders either at the site of action potential initiation or in the pathways for action potential conduction. Ischaemic heart disease, in which there is a reduced local blood flow within the heart, is a common cause of arrhythmias.

If the discharge rhythm of the SA node is depressed the AV node, or more usually a *latent pacemaker*, assumes pacemaker function and drives the heart at a *lower frequency* than usual. These latent pacemakers are usually found in or close to the conduction system in both atria and ventricles. If this new pacemaker is in the AV node or in the ventricles, there could be occasions where both atria and ventricles depolarized at the same time. The consequence of this will be that atrial contraction will occur during ventricular contraction when the AV valve would be closed.

In the conducting system the AV node is the most susceptible to damage, developing a very slow initial depolarization and prolonged action potential. This decreases the speed of conduction through the AV node and, depending on the severity, causes a *longer interval* than usual between atrial and ventricular contractions or a partial or a complete heart block. In *partial heart block* the atria beat normally but only some of the atrial action potentials reach the ventricle. The block may be regular, i.e. 2 to 1 or 3 to 1, in which case every second or third action potential respectively reaches the ventricle - or it may be irregular. The action potentials that did not reach the ventricles arrived at the AV node when it was refractory. A partial heart block may be evident in a normal heart when it is driven by sympathetic stimulation powerful enough to cause very high atrial rates. In *complete heart block* the AV node fails to transmit impulses. The atria beat at the rhythm dictated by the SA node and, because of compensating reflexes, this may be faster than usual whilst latent pacemakers in the ventricle initiate their own rhythm somewhere between 20 to 40 beats per min. A transient complete heart block can occur during powerful parasympathetic stimulation which blocks the AV node.

Latent pacemakers may develop pacemaker potentials in the absence of damage to the SA or AV nodes and become sites known as *ectopic foci.* If these develop in the atria, their depolarization may occasionally reach threshold (when the atria are not refractory from a normal beat) resulting in an occasional extra atrial contraction and hence an *extra ventricular contraction (extrasystole).* This excitation will rapidly depolarize the SA node which must repolarize and then depolarize before it can initiate the next normal beat. Consequently, the pause between the extra beat and the next normal beat is slightly longer than the usual beat interval. In *paroxysmal atrial tachycardia* the atrial ectopic foci discharge at a higher frequency than the SA node (often only intermittently) and drive the heart at rates up to 220/min. In *atrial flutter* the ectopic foci discharge at rates of 200 to 350/min causing rapid regular atrial contractions. However the AV node cannot transmit every atrial action potential and thus some degree of partial heart block results. In *atrial fibrillation* the multiple ectopic foci simultaneously discharge asynchronously at rates of 300 to 500/min to give feeble atrial contractions. More importantly, the ventricle contracts at a totally irregular rate often before it is adequately filled with blood.

When the ectopic foci develop in the ventricles, the arrhythmias are more serious. If the ectopic foci reach threshold at any time between the end of the refractory period of the usual action potential and the beginning of the next regular action potential, it will trigger an extra action potential causing an early *extra ventricular contraction.* This is a weaker contraction than usual because the action potential will be of shorter duration and because insufficient time will have been allowed for ventricular filling. The extra ventricular excitation will render the ventricular muscle refractory at the time the next SA discharge occurs. Hence the next atrial contraction occurs but the next beat is missed. The *compensatory pause* resulting from the missed beat is nearly two normal beat intervals. The succeeding ventricular contraction will be large because of the extra time allowed for ventricular filling. The electrical event from the ventricles rarely propagates retrogradely. The extra ventricular beats may be isolated and irregular or occur rather regularly. If the ventricular ectopic foci discharge at a high regular frequency, they cause *paroxysmal ventricular tachycardia.* If there are multiple ectopic foci in the ventricles discharging at a high rate, then rapid, uncoordinated and ineffective ventricular contractions (*ventricular fibrillation*) ensue causing death. Sympathetic stimulation to the heart can increase the tendency of ventricular fibres to develop ectopic foci. Ventricular fibrillation can sometimes be treated successfully by electric *defibrillation* in which the heart is exposed to a brief burst of external electric current. This depolarizes instantly the entire myocardium and hopefully the myocardium will then repolarize as a coordinated unit without redeveloping fibrillation.

Arrhythmias can also occur because of unequal conduction velocities through branches of the conduction system. One branch (b) conducts normally but the damaged one (C) has a long refractory period and a slow conduction velocity. When the action potential arrives at A it can only propagate through B but because of the syncytial organization of the heart it can arrive again at C when C is no longer refractory and propagate retrogradely through C to the original starting point, A. Because of this long pathway, the action potential arrives at A when it is no longer refractory and hence A is immediately re-excited. The action potential propagates back down B and again enters C retrogradely setting up a circular patter of depolarization and causes a frequency of contractions greater than normal. This *circus movement* can initiate atrial and ventricular fibrillation and possibly cause paroxysmal atrial and ventricular tachycardia and atrial flutter. Arrhythmias caused by circus movement are often referred to as *re-entry arrhythmias.*

Electrocardiogram

The combined effect of the myocardial action potentials during each heart beat produces a voltage which is present throughout the whole body. By placing electrodes on the surface of the body the differences in this voltage (about 1 mV) between electrodes can be recorded and amplified. This is the electrocardiogram (ECG). It is conventional to regard the heart, which is oriented to the left, as situated in the centre of an isosceles trianglee, the *Einthoven triangle,* with the upper corners corresponding with the shoulders and the lower corner with the pubis. Recording electrodes, when attached to right and left arms (RA and LA) and to one or other

foot, conventionally the left (LF), are effectively placed at the corners of this triangle and examine the heart vertically (coronal plane).

The recording electrodes (referred to as leads) fall into three categories: standard limb leads, augmented limb leads and chest leads. From *standard limb leads* bipolar recordings are obtained between any two corners of the triangle either between LA and RA (lead I) or between LF and RA (lead II) or between LF and LA (lead III) with a fourth electrode on the right foot acting as an earth. From *augmented limb leads* unipolar recordings are obtained, one of the three corners of the triangle acting as the active (positive) electrode, the remaining two leads connected together as the indifferent (negative) electrode and the right foot earthed. When the active electrode is the RA, LA or LF the lead is designated aVR, aVL or aVF respectively. The term aV refers to the augmented voltage (about 50% more) obtained by these leads compared with standard limb leads.

Chest leads give unipolare recordings with the active electrode in one of six positions on the chest, the indifferent electrode consisting of the LA, RA and LF connected together and with the right foot earthed. Lead V_1 is placed over the fourth intercostal space near the sternum on the right, V_2 is in a similar position on the left, V_3 is on the left midway between V_2 and V_4, V_4 is over the left fifth intercostal space in the mid-clavicular line, V_5 and V_6 are over the same space but in the anteriro axillary line and mid-axillary line respectively. Electrodes placed on the chest examine the heart horizontally not vertically.

The pattern of the ECG obtained varies with different leads but certain basic features are always present. The *P wave* is produced by the spread of electrical activity during atrial depolarization. The *QRS complex* is produced by ventricular depolarization and the *T wave* by ventricular repolarization. When no depolarization or repolarization is occurring there is zero voltage difference in the ECG (the *isoelectric line*). Atrial repolarization does not produce any detectable wave because it occurs during the QRS complex. Since ventricular repolarization is less well synchronized than ventricular depolarization the T wave is longer in duration but smaller in amplitude than the QRS complex. The *PQ* or *PR interval* is the time required for excitation to spread through the atria, AV node and bundle of His. The *QS interval* is the time required for excitation to spread through ventricles. The *QT interval* is a measure of the duration of the ventricular action potential and is closely related to the duration of ventricular contraction. Depending on the lead, the QRS complex may have one or two or sometimes three components. If the first deflextion from the isoelectric line is negative (by convention downwards) it is called a Q wave. If positive it is called an R wave and if the next deflection falls below the isoelectric line it is called an S wave.

At a given electrode, the polarity of the potential change depends on the direction in which the wave of *depolarization* is moving in the heart. By convention, if the wave is travelling towards the electrode, a positive potential is recorded and if the wave is travelling away from the electrod a negative potential is recorded. A wave of repolarization travelling towards or away from the electrode causes a

negative or positive potential respectively. At any instant, the total electrical activity can be though of as a vector having both direction and magnitude.

Depolarization of the atria commences at the SA node and spreads through atrial muscle to the AV node. The net result is a vector directed downwards and to the left (P wave). Ventricular depolarization starts in the interventricular septum which depolarizes from left to right, resulting in a vector directed downwards and to the right (phase 1 of the QRS complex). Depolarization then spreads through the ventricular muscle from inner to outer surface. Since the left ventricle has more bulk than the right, the mean direction of the vector is downwards and to the left (phase 2 of the QRS complex). The last segments of the myocardium to be activated are the upper septum and the high posterior walls resulting in a vector directed upwards and to the right (phase 3 of the QRS complex). Ventricular repolarization spreads from the outer to the inner surface of the ventricular myocardium. Since it is opposite in both direction and sign from phase 2 of the ventricular depolarization, it produces a vector in the same direction, i.e. downwards and to the left (T wave).

The direction of these vectors and the position of the limb lead in relation to the Einthoven triangle determine the size and polarity of the ECG waves. Each lead can be regarded as 'looking' at the heart in a particular direction. Standard limb leads look from the positive to the negative electrode, augmented limb leads look at the heart from the limb by which they are named and both types look in a vertical plane. Lead II normally looks most directly at the main vectors and therefore has the largest as well as positive P, R and T waves with negligible Q and S waves. In leads I and aVF the deflections are all positive but of smaller amplitude than lead II because they do not look so directly at the main vectors. Leads III and aVL look at the heart sideways and detect best the vectors associated with interventricular septal depolarization (phase 1 and 3 of the QRS complex). This vector moves towards lead III causing a small positive R wave and away from the lead aVL causing a negative Q wave. Neither lead III nor aVL detect the P wave well and the T wave is very small and positive. Lead aVR is the only one looking at the heart backwards such that the main vectors are moving away from the electrode. Thus P and T waves are negative and the QRS complex is seen as a large negative Q wave.

Chest leads give larger ECG deflections than limb leads and look at the heart in a horizontal plane. The P and T waves are positive in all leads except V_1 which is to the right of the heart and hence sees the vectors moving away. The P and T amplitudes depend on how directly the V_2 to V_6 electrodes look at the P and T vectors. Leads V_1 and V_2 show a small positive R wave and large negative S wave. Lead V_4 shows a small Q and S wave and a large R wave (the full QRS complex) and leads V_5 and V_6 show mainly a large R wave in the QRS complex.

The direction of the vector at any instant is the electrical axis of the heart at that instant. The *mean electrical axis* is defined as the direction of the largest vector in the vertical plane (usually lead II) and since it correlates well with the long axis of the heart (i.e. the interventricular septum) it can be used to infer whether the orientation of the heart is normal. Tall, thin people tend to have a more vertical heart and the mean electrical axis lies between leads II and aVF. Hypertrophy of one

ventricle with respect to the other will move the mean electrical axis to right or left of normal. The chest lead that gives equal amplitude R and S waves (usually V_3) overlies the anterior edge of the interventricular septum and is said to mark a *transition point.* Rotation of the heart in the horizontal plane also depends on body build and occurs with hypertrophy of one ventricle and can be detected as a right or left shift of the transition point.

Cardiac Cycle and Heart Sounds

The interrelationships amongst electrical, mechanical (pressure and volume) and valvular events during one complete heart beat, referred to as the *cardiac cycle,* are illustrated. Events on both sides of the heart are similar though slightly asynchronous. The organization of the electrical conduction system is such that the contraction of the right atrium precedes that of the left atrium and the left ventricular contraction precedes that of the right ventricle. However right ventricular ejection begins before the left ventricular ejection because pulmonary arterial pressure is lower than the aortic pressure. Furthermore, since the pulmonary circuit is less resistant to blood flow than the systemic circuit, the right ventricular ejection goes on for longer and hence the pulmonary valve closes after the aortic valve.

At a resting heart rate of 70/min each cardiac cycle last 0.85 sec and is composed of two periods: *systole,* when the ventricles contract and eject blood into the aorta or pulmonary artery, and *diastole,* when the ventricles are relaxed and fill with blood from the veins. The duration of ventricular muscle contraction and thereafter by definition, systole, is 0.3 sec. Diastolic filling occupies almost two-thirds of the cycle (0.55 sec) at rest. However, when the heart rate increases to its 200/min maximum, the total cycle is reduced to 0.3 sec. A reduced duration of the action potential can shorten systole to about 0.15 sec, leaving only 0.15 sec for diastolic filling.

It is convenient to begin describing the cardiac cycle prior to atrial contraction, i.e. in *mid-diastole.* At this point both atrial and ventricular pressures are low but, since atrial pressure is slightly greater, blood from the veins entering the atria flows on into the ventricles through the open AV valves. The ventricles are already nearly 80% full and this venous inflow is small in volume. As diastole continues both atrial and ventricular pressures slowly increase as the chambers are filled because, since the aortic and pulmonary valves are closed, blood enters but cannot leave the heart. At this stage the aortic pressure remains high for reasons which will be explained later.

In *late diastole* the P wave of the ECG occurs, reflecting atrial depolarization. Towards the end of the P wave the atria begin to contract causing an increase in atrial pressure (the *a wave*) which propels most of the blood within the atria into the ventricles. The addition of this final 20% to ventricular filling is accompanied by a small increase in ventricular pressure. As the atria begin to relax, atrial and ventricular pressures drop slightly. The volume contained in each ventricle at the end of diastole (about 130 mL when standing and about 160 mL when lying) is the *end-diastolic volume.*

Towards the end of diastole the QRS complex of the ECG begins indicating ventricular depolarization and, by the end of the QRS complex, the ventricle starts to contract. In this *early systole* the ventricular contraction generates an immediate increase in ventricular pressure which rapidly exceeds atrial pressure. This causes the AV valves to shut, setting up vibrations in these valves which are transmitted to the chest wall and can be heard with the aid of a stethoscope (*first heart sound*). With microphones and recording apparatus (phonocardiography), the waves composing this low-pitched sound can be displayed.

As the ventricles continue to contract with their chambers closed, both the tension in the ventricular wall and the pressure in the ventricular lumen increase markedly. This is associated with vibrations in the ventricular muscle fibres which contribute to and prolong the first heart sound. Since blood can neither enter nor leave the ventricle, this period is referred to as the *isovolumetric* or *isometric phase of ventricular contraction*. Because of the high ventricular pressure, the AV valves bulge back into the atria causing a sharp rise in atrial pressure to about 10 mmHg (left atrium) or 5 mmHg (right atrium) - the *c wave.*

In *mid-systole* when the ventricular pressure first exceeds aortic pressure, the aortic and pulmonary valves open and blood is accelerated and ejected very rapidly from the ventricles into the arteries. Their pressures follow very closely the ventricular pressures and rise from their diastolic minima of 80 mmHg (systemic) or 8 mmHg (pulmonary) to their systolic peaks of 120 mmHg (systemic) or 25 mmHg (pulmonary). During this rapid ejection phase the shortening of the ventricles pulls the AV fibrous ring downward and, since the venous openings into the atria are in a fixed position, the effect is to lengthen the atria and increase their capacities. Thus there is a sudden fall in atrial pressure, often to negative values, but never as subatmospheric as the intrapleural pressure.

In mid-systole the T wave of the ECG reflects repolarization. Towards the end of the T wave, in *late systole,* the ventricular muscle starts to relax and ventricular pressures drop. Ventricular pressure actually drops below aortic pressure but blood continues to be ejected slowly because of the momentum imparted to it during the initial acceleration earlier in systole. In the aorta, pressure does not drop as quickly as ventricular pressure because, owing to the resistance to flow through peripheral arterioles, only about a half of the ejected volume has been propelled through the aorta. The remainder has been accommodated in the aorta by stretching its elastic elements. As the rate of ejection into the aorta slows, the stretched aorta elastically recoils, propelling blood onwards to the arteries. In addition at the end of ejection there is a small transient retrograde aortic flow towards the ventricles which causes the aortic valve to close. The volume contained in each ventricle at the end of systole is called the *end-systolic volume* and is about 60 mL when standing. Thus about 70 mL (the *stroke volume*) was ejected in systole. The proportion of the end-diastolic volume that is ejected (i.e. stroke volume / end-diastolic volume) is the *ejection fraction.*

Since all valves are now closed, no blood can enter of leave the ventricles and this period of rapid ventricular relaxation and rapidly falling ventricular pressure is called the *isovolumetric* or *isometric phase of ventricular relaxation*. During this period

the *second heart sound* (a quicker and higher-pitched sound than the first) is heard. It is generated by the vibration from closure of aortic and pulmonary valves. This sound is often split, especially during inspiration, because the aortic valves closes slightly before the pulmonary valve. The pressure wave associated with the closure of the aortic valves is reflected along the aorta giving rise to the *incisura.* Throughout systole the atrial pressure has gradually increased from below zero to a peak of about 5 mmHg (left atrium) or 2 mmHg (right atrium) at the end of the period of isovolumetric relaxation - the *v wave.* This gradual increase in atrial pressure results from the continuous venous return accumulating in the atria against closed AV valves and from the return of the AV fibrous ring to its resting position in mid-systole.

At the beginning of *early diastole* ventricular pressure has just dropped below that of the atria and the AV valves open. The ventricles fill rapidly with blood that has accumulated in the atria, setting up vibrations sometimes detectable as the *third heart sound.* During this rapid filling both atrial and ventricular pressures decline. They then gradually increase in mid-diastole as ventricular filling continues slowly (*diastasis*) as a consequence of venous flow into chambers closed by aortic and pulmonary waves. Throughout diastole atrial pressure is slightly greater than ventricular pressure. The rapid initial filling of the ventricles early in diastole is very important because it means that when heart rates are high and the diastolic period short, ventricular filling will lose only the contribution from the later diastasis. Similarly the rapid large volume ejection early in systole prewvents a short duration systole from markedly restricting stroke volume. Throughout diastole the aortic pressure remains high due to the continuing elastic recoil of aortic walls stretched during the previous systole. However there is a slow decline to a diastolic minimum as the blood flows from the aorta into the rest of the vascular system.

Abnormal Heart Sounds

A *fourth heart sound* can be heard just before the first heart sound if vibrations are set up during the rapid ventricular filling associated with atrial contraction. These vibrations occur whenever the atrial pressure is high or the ventricle stiff as in ventricular hypertrophy.

Abnormal sounds called *murmurs* can occur at any stage of the cardiac cycle. If blood passes through a narrowed orifice or regurgitates back into a chamber, its flow becomes turbulent and this may generate murmurs. Pathological narrowing of an orifice is referred to as *stenosis.* Stenosis of the atrioventricular orifice results in turbulent flow into the ventricles (*diastolic murmur*) and stenosis of the aortic or pulmonary artery (*systolic murmur*). If a valve is *incompetent,* this results in a backflow of blood. Incompetent AV valves allow systolic regurgitation into the atria (systolic murmur) and incompetent aortic or pulmonary valves cause diastolic regurgitation into the ventricles (diastolic murmur). Defects in the atrial or ventricular septum also cause systolic murmurs while a patent ductus arteriosus connecting the aorta with the pulmonary artery can be associated with a *continuous murmur* throughout the cardiac cycle. Frequency, character, duration, time of occurrence in the cardiac cycle and the site on the chest from which the murmur is heard most clearly frequently enable one to diagnose the underlying abnormality.

Jugular Venous Pulse

Since there are no valves at the entry of the venae cavae into the right atrium, the three positive a, c, and v waves in the right atrial pressure are transmitted backwards into the large veins. They can be seen as pulsations in the jugular vein in the neck and are called the *jugular venous pulse (JVP).* Because they are transmitted backwards from the atrium, each wave in the JVP occurs after the corresponding one in the atrium. The *a wave* of the JVP occurs because of atrial contraction but it is not just a delayed reflection of the increase in atrial pressure. It is also contributed to by the damming of blood in the large veins resulting from the atrial contraction constricting the orifices of the venae cavae. The *c wave* is a delyed reflection of the increase in atrial pressure when the AV valves bulge into the atria. The pressure pulse transmitted from the adjacent carotid artery during peak systole also makes a contribution. Hence the name *c wave.* The *v wave* has the same origin as the v wave in the right atrial pressure. The relative amplitudes of the JVP waves are variable because the jugular vein is subjected to rhythmical pressure fluctuations induced by breathing which occur at a rate much slower than the heart beat. The shape and magnitude of the JVP can indicate the presence of cardiac arrhythmias, valvular incompetence and stenosis.

Mechanical Characteristic of Cardiac Muscle

Length-tension curves and *load-velocity curves* can be used to study the mechanical characteristics of strips of cardiac muscle and these curves are basically similar to those of skeletal muscle. Muscles have both elastic and contractile elements which are stretched passively, generating a *passive tension* whenever the muscle length is extended. When the cardiac muscle contracts and shortens under a constant load, the contraction is referred to as *isotonic.* Here the contractile elements shorten without any change in tension.

If the muscle length is kept constant as it contracts (an *isometric* contraction) the elastic elements stretch as the contractile elements shorten and the muscle develops a *total tenion.* This total tension is composed of the *active tension* generated during contraction plus the already present *passive tension.* The active tension developed depends on the initial length of the muscle. Unless the muscle becomes overstretched, differences in length which do not alter passive tension appreciably will result in large difference in active tension. As in skeletal muscle this reflects the degree of overlap of actin and myosin filaments and the resulting numbers of crossbridges. In contrast to skeletal muscle, where the resting length is close to the optimal length, the resting length of cardiac muscle is below optimal and thus cardiac muscle is always operating on the ascending part of the length-tension curve. This intrinsic ability of cardiac muscle to contract more powerfully whenever it is stretched over its physiological range is the basis of the *intrinsic control of stroke volume* considered later.

Since the myocardium is an electrical network, the strength of contraction for a particular initial muscle length cannot be graded by recruitment of a variable number of motor units as occurs in skeletal muscle. In cardiac muscle the strength

of contraction can be increased by the higher frequency of cardiac action potentials occurring when heart rate increases or, most importantly, by increasing the membrane conductance to Ca. Both these increase the intracellular Ca available for the contractile process. Changes in the strength of cardiac contraction are called positive or negative *inotropy*.

Sympathetic stimulation and circulating adrenaline acting via beta1 adrenergic receptors increase the heart rate, reduce the duration of action potentials and increase the conductance for Ca ions. The considerable increase in total tension developed for any particular muscle length caused, for example, by adrenaline is illustrated. This is referred to as an increase in *myocardial contractility* and is the basis of the *extrinsic control of stroke volume.*

Parasympathetic stimulation acting via muscarinic cholinergic receptors decreases the heart rate, increases the duration of action potentials and decreases conductance for Ca ions. This diminishes appreciably the strength of atrial contraction. Until recently the ventricles have been considered to be devoid of parasympathetic innervation but, providing there is a background of tonic sympathetic activity, a depressant effect of parasympathetic stimulation on the strength of ventricular contractions can be demonstrated. Myocardial contractility is also depressed during cardiac failure and by the direct action of acidosis, hypercapnia and severe hypoxia.

The amount of passive tension in a muscle prior to its contraction is referred to as the *preload* and in the heart as a whole is related to the end-diastolic volume. If the muscle has to support an extra weight (called the *afterload*) after it has started contracting, it will first develop sufficient isometric tension to match the total load and then shortens, lifting the afterload in an isotonic contraction. As in skeletal muscle if the afterload is increased, the velocity of this isotonic contraction fo r a particular afterload decreases in an exponential curve as illustrated by a *load- velocity curve.* In the heart as a whole the aortic pressure can be regarded for the left ventricle as the equivalent of its afterload and it determines the total tension developed during systole.

When an isolated strip of cardiac muscle is stretched before its contractile responses to different afterloads are tested, this increased preload increases the velocity of shortening for any afterload, particularly with the larger afterloads as well as causing a more powerful contraction. Adrenaline increases the velocity of shortening for any afterload, particularly for the smaller afterloads, as well as causing a more powerful contraction.

Control of Stroke Volume

By analogy with length-tension curves for strips of cardiac muscle, *volume-pressure curves* can be constructed for the heart. Length is now analogous to ventricular volume, passive tension to diastolic ventricular pressure and total tension to the maximum systolic ventricular pressure that could be developed at each volume. During diastole the heart fills with blood increasing in volume from an end-

siastolic volume (ESV) of 60 mL to an end-diastolic volume (EDV) of 130 mL with an increase in left ventricular pressure from about 5 mmHg at A to about 10 mmHg at B. During the isovolumetric (i.e., isometric) phase of ventricular contraction the pressure increases to C. If the aorta was clamped, since blood cannot escape, the pressure would continue to rise to C^* on the curve for maximum systolic ventricular pressure. Note that for a normal EDV, C^* is well to the left of the maximum peak.

In a normal cardiac cycle the isovolumetric phase of ventricular contraction terminates when the semilunar valve opens (at pressure C) and the volume begins to decrease. The pressure at C will depend on the diastolic pressure in the aorta or pulmonary artery. For the left ventricle this is about 80 mmHg and during the ejecion of blood the pressure increases to about 120 mmHg and then declines to about 100 mmHg at D. From C to D the contraction is referred to as *auxotonic* occurring against the afterload of increasing aortic pressure. When the aortic valve closes, isovolumetric ventricular relaxation occurs and the pressure drops from D to A. The *area* enclosed by this volume-pressure loop (ABCDA) is a measure of the *external work* done by the heart each beat.

Intrinsic Control of Stroke Volume

The volume-pressure curves and the concept of the work loop were first described in 1895 by Frank using an isolated frog heart in which the aorta was clamped nd the ventricles filled to different volumes between each beat. In 1914 Starling and his colleagues developed a mammalian heart-lung preparation in which the pulmonary circuit was intact and the lungs mechanically ventilated (to keep the heart supplied with O_2) but the systemic circuit was replaced by a system of blood-filled tubes. The diameter of these tubes could be decreased to increase resistance and hence increase aortic pressure (afterload) and the height of the reservoir returning blood to the heart could be elevated to increase the filling pressure and hence increase diastolic volume (preload).

An increase in EDV (preload) causes the heart to begin its isovolumetric contraction at a higher pressure and volume (position B'). Thus the new volume-pressure loop is larger but with pressures C', D' and A' only slightly elevated. The ESV is slightly increased but the heart now operates at a larger EDV and ejects a larger stroke volume at a higher ejection velocity. The relationship which is obtained between each EDV and the resulting stroke volume is often referred to as the *Starling curve* or ventricular function curve and it illustrates the so-called *Frank-Starling law of the heart*. This states that the heaart has an intrinsic ability to regulate its stroke volume, responding with a greater force of contraction to the stimulus of increased diastolic stretch. The upper limit to this intrinsic ability is reached when the enlarged EDV has resulted in an optimal myocardial lengh. The term *heterometric autoregulation* has been used to describe this. Heterometric indicating that the autoregulation is a consequence of the alteration in the initial myocardial fibre length.

An increase in aortic pressure (afterload) in the heart-lung preparation requires that an equal increase in ventricular pressure must occur before the aortic valve can open (position C'). Thus with the remaining energy of this contraction the stroke

volume is smaller in the first ejection agains the increased afterload. Hence the ESV increased and with normal venous return the EDV subsequently increases, stretching the ventricle so that at the next contraction more tension is developed nd so on until a new steady state is reached. The final volume-pressure curve is shifted to the right and up. The loop has a larger area, indicating more work, and the heart operates with a larger ESV and EDV but with an unchanged stroke volume. However this intrinsic mechanism of compensation for an increased afterload is limited and with larger increases in afterload the eventual response is a decreased stroke volume, large EDV and ESV and a short ejection phase with decreased ejecion velocity.

When cardiac output is plotted against mean rightt atrial pressure, the Starling graph is often called a *cardiac function curve.*

The intrinsic control of stroke volume operates whenever here is a change in diastolic filling of the ventricles. Its primary function is to correct any *momentary imbalance of the cardiac outputs of the two ventricles.* Since the two ventricles beat at the same rate, their outputs can only be matched by adjusting their stroke volumes. Imbalance between the systemic and pulmoary circuits can occur as a result of change in the arteriolar resistance (afterload) or a change in the volume of blood returned to the heart (preload) by one circuit but not the other. Indeed, the latter normally happens throughout the respiratory cycle, with a larger right and a smaller left stroke volume during inspiration and the converse during expiration.

Intrinsic control is also important when systemic *venous capacity* changes. For example, the volume contained in the systemic venous system is decreased when reclining compared wih standing. This results in a greater central blood volume in the heart and lungs and the increased EDV leads o an increased stroke volume. Reflex contraction of smooth muscle in the veins also decreases venous capacity, for example in response to haemorrhage or in exercise where the effect is augmented by the skeletal muscle venous pump. Decresed venous capacity contributes slightly to the increased EDV of exercise in the upright posture. Acute increases or decreases in *total blood volume* (transfusion or haemorrhage) also increase or decrease the EDV and hence alter stroke volume accordingly.

Factors Influencing End-Diastolic Volume

The EDV can be decreased by *very high rates* which reduce the time available for the slow diastolic filling phase (diastasis). However, since the increased sympathetic activity also causes a distinct increase in the rate of ventricular relaxation, much of the loss of diastasis is compensated for by the rapid *relaxation recoil of th ventricles,* increasing the volume achieved in the initial rapid diastolic phillling phase. An increase in the power of *atrial contraction*, for example during exercise, increases EDV by increasing the a wave of atrial pressure and heencee the atrial contribution to ventricular filling.

A larg increas in *atrial pressure* at any other time in the cardiac cycle reduces the pressure gradient and hence blod flow from the capillaries to the atria and this will tend to limit increases in EDV. Similarly an elevated *ventricular pressure* during diastole will restrict further filling of the ventricles. Reduced distensibility or

compliance of the ventriclees caused by hypertrophy or fibrosis or by accumulation of fluid in the pericardial space (cardiac tamponade) will result in a smaller EDV for any particular diastolic ventricular pressure.

Finally, the surrounding *intrathoracic pressure* (or intrapleural pressure) influences EDV. This pressure is subatmospheric. At rest it is about - 3 mmHg and about - 5 mmHg in inspiration but it becomes positive in large expirations and more negative in large inspirations. The more negative the intrathoracic pressure the greater is its dilating effect on the ventricles and atria. Thus here is a greater diastolic filling during inspiration than expiration. However, because there are valves in the veins preventing retrograde flow, large expirations do not reduce diastolic filling appreciably.

Extrinsic Control of Stroke Volume

In the 1950s, Sarnoff investigated the effect of *adrenaline* and *sympathetic* stimulation on the heart-lung preparation and demonstrated that the maximum systolic pressures which could be generated for any EDV were increased and in proportion to the degree of stimulation. This is the positive *inotropic* effect of the sympathetic nervous system, increasing *myocardial contractility* and increasing ejection velocity. Parasympathetic stimulation has a negative inotropic effect but the extent of this and its importance is not clear. A reflex increase in sympathetic activity to the heart occurs during exercise, during situations when the mean arterial pressure has decreased, for example in haemorrhage, and when blood flow is inadequate for O_2 and CO_2 homeostasis, as may occur, for example, if the cardiac output is not maintained against a high afterload.

The positive inotropic effect results in two types of volume-pressure loops, one leading to an increase in the stroke volume and one maintaining a normal stroke volume despite an increase in afterload. In the first situation, for the normal EDV and end-diastolic ventricular pressure (B) and only a slightly larger than normal aortic diastolic pressure (C'), the shift of the maximum systolic pressure curve to the left allows position D' to move to a higher pressure and a very much lower volume. Thus the ESV at A' is reduced and a large stroke volume has been ejected. I will occur at a higher ejection velocity. Since there is no change in initial myocardial fibre length (i.e., EDV is constant), this extrinsic control of stroke volume is also referred to as *homeometric regulation.* If the effects of different degrees of sympathetic activity and hence of myocardial contractility on stroke volume are examined over a range of EDVs a family of Starling curves can be plotted.

In the second situation, if sympathetic stimulation has also caused an increased afterload as a result of constriction of the arterioles, the increased myocardial contractility will permit he high pressure of C' and D' to be reached without any change in EDV or ESV. Thus the stroke volume and its ejection velocity are normal. Usually, the compensation for an increased afterload is a mixture of intrinsic and extrinsic control of stroke volume.

Since the maximum systolic pressure curve would be difficult to measure clinically, an index of ventricular contractility is used. One such index is the measurement with a cardiac catheter of the maximal rate of pressure increase during the isovolumetric phase of ventricular contraction. A measurement of stroke volume itself would be an insufficient index as stroke volume depends on preload, afterload and the competence of valves, as well as on contractility.

Law of Laplace and the Heart

Length-tension curves of strips of cardiac muscle and volume-pressure curves of the whole heart are not identical because volume is proportional to length^3 (or radius^3) and the tension within the muscle is not identical to the pressure in the chamber lumen. The relationship between wall tension and lumen pressure is described by the *law of Laplace.*

For hollow spherical organs the total circumferential wall tension depends on the tension per unit length (*T*), the two equal radii of curvature (*2r*) and the thickness of the wall (*u*) and equals *Tp2ru*. The total lumen pressure depends on the transmural pressure per unit area (P_t) and the radius of he lumen (*r*) and equals $P_t pr^2$. *Transmural pressure (P_t)* is the pressure per unit area on the inside of the wall minus the pressure per unit area on the outside of the wall. At equilibrium the total tension and total pressure counterbalance one another, hence $Tp2ru = P_t pr^2$. Thus the law of Laplace states:

$$\boldsymbol{P_t = 2Tu/r} \text{ or } \boldsymbol{T = P_t r/2u.}$$

With the law of Laplace a number of properties of the heart can be explained:

(i) The rise in ventricular pressure during the ejection phase (C to D) is due not to increasing the strength of muscle contraction but to the physical effect of a change in heart size. As the radius get smaller and the wall thicker, additional ventricular pressure is generated for the same tension in the ventricular wall.

(ii) In an excessively dilated heart the large radius and thin walls contribute, together with the overstretching of the actin and myosin, to the decline in the maximum systolic ventricular pressure.

(iii) An excessively dilated heart caused, for example, by congestive cardiac failure, has to generate more total wall tension to develop the same systolic ventricular pressure than does a normal heart. This extra tension requires more O_2 consumption a a time when O_2 is being insufficiently transported by the whole cardiovascular system and when the high cardiac wall tensions are compressing the coronary arteries more and for a longer period within the cardiac cycle.

(iv) In trained athletes or in the chronically volume- or pressure-loaded heart hypertrophy of the heart develops. This increase in myocardial wall thickness can compensate for the increased chamber dilatation allowing a given pressure to be generated by the usual wall tension. However, since the cardiac hypertrophy in the

loaded heart in contrast to that of the trained athlete is not accompanied by new cardiac capillaary formation, this often leads to insufficient O_2 delivery to the cardiac muscle.

Cardiac Output and Its Measurement

Cardiac output is the volume of blood pumped per minute by each ventricle and is thus the total blood flow through the pulmonary or systemic circuit. It is the product of *stroke volume (volume per beat)* and *heart rate (beats per minute).* Increments in heart rate contribute more than stroke volume to the cardiac output of exercise. The maximum heart rate and the minimum ESV are the same for non-athletes and trained athletes. Hypertrophy of the heart in the trained athletes allows their resting heart rate to be lower and their maximum cardiac output to be higher. Athletes can therefore supply more O_2 per minute to skeletal muscle and perform greater levels of exercise.

Cardiac output (*Q*) can be measured by inserting flowmeters into the aorta or placing electromgnetic flowmeters or ultrasonic flow probes around the whole of the aorta. Clinically two alternative methods are used. The *Stewart-Hamilton indicator dilution technique* involves injecting rapidly a dye or radioactive isotope or cold saline into the venous circulation near the heart. The indicator quickly mixes with the cardiac contents and during the nextt few beats the entire blood-indicator mixture is pumped out of the heart into the circulation. The concentration of this mixture is measured by continual sampling from an artery in the arm for one complete circulation (about 3-40 s at rest). The mean concentration of the mixture for one complete circulation is determined and

Q = amount of indicator /(mean conc x duration of one circulation)

The second method uses the *Fick principle.* This states that the amount of a substance taken up by an organ (or the body) per unit time is equal to the arterial concentration minus the venous (mixed) concentration of that substance. In practice, the average steady-state oxygen consumption of the whole body is measured for bou 15 min, during which time blood samples are taken from a systemic artery and the pulmonary artery (the latter contains mixed venous blood). The arterial and mixed venous O_2 contents are aanlyzed. Then

Q = V / (A'-V').

Stroke volume can be determined from these cardiac output measurements by dividing the average heart rate (from an ECG record or arterial pulse). With new techniques, stroke volume itself can now be measured by non-invasive procedures of impedance cardiography, echocardiography and radionuclide imaging.

11.3 The Vascular System

Physics of Blood Flow (Pressure, Resistance and Velocity)

Liquid flows through a rigid tube from a higher to a lower pressure and the *rate of flow* (V, volume/unit time) is directly proportional to the *hydrostatic pressure gradient* (delta P). In the vascular system blood pressures are usually expressed in mmHg although other units are also used (l mmHg = 13.6 mmH_2O = 133 Pa). The *resistance* (R) to blood flow depends upon the dimensions of the tube and the viscosity of the blood. The greater this resistance the slower the rate of flow. These determinants of flow can be summarized in an equation analogous to Ohm's law for electrical circuits:

$$V = \Delta P / R.$$

If V and deltaP are in units of litres/min and mmHg respectively, then the calculated values of R have the units mmHg/Lmin.

Resistance results from the friction (or viscous forces) between the molecules or particles of the liquid as they move and from the friction between this liquid and the walls of the tube. During steady flow an infinitely thin layer of fluid in contact with the wall does not move whilst the next layer moves slowly with the central axis layer moving at the fastest rate. Such layered or *laminar flow,* parallel to the axis of the vessel, has a parabolic velocity profile. The concept of viscosity (ç) of a liquid expresses the fact that the adjacent layers interact rather than slip with infinite ease over one another. The greater the liquid's viscosity the greater the resistance to flow.

Since the friction is greatest between the liquid and the tube wall, the dimensions of length (l) and radius (r) of the tube affect the resistance to flow. The longer the tube or the smaller the radius of the tube the greater is the resistance offered. These determinants of resistance can be summarized in the following equation:

$$R = 8çl / ðr^4.$$

A two-fold decrease in radius will cause a sixteen-fold increase in resistance and resistance is affected more by changes in vessel radius than by changes in length or in viscosity.

In an unbranched tube the relationships amongst blood flow, the pressure gradient and the determinants of resistance are described by the *Hagen-Poiseuille equation:*

$$V = \Delta P ðr^4 / 8çl.$$

In any blood vessel the length is virtually constant, the viscosity is relatively constant and flow through it can be increased only by increasing its radius or the pressure gradient or both. Only arterioles show marked changes in radii which will affect resistance. An increase in flow through other types of blood vessels requires

an increase in the pressure gradient. The Hagen-Poiseuille equation also indicates that at a constant flow an increase in radius of the arterioles will result in a decrease in the pressure gradient along the arteriole. This affects the pressure upstream (arteries) and downstream (capillaries).

In the systemic vascular system it is important not only to consider an individual vessel but also an entire network. If the vessels are arranged *in series,* the total resistance to flow is the sum of all the individual resistances, whereas if they are arranged *in parallel,* the reciprocal of the total resistance is the sum of all the individual reciprocal resistances. Therefore for vessels in parallel the total resistance is considerably smaller than the resistance of each individual vessel. Arteries, arterioles, capillaries, venules and veins are in general arranged in series with respect to each other. However the vascular supply to various organs and the vessels within any organ are arranged in parallel.

In a series arrangement the same volume / unit time (V) will flow sequentially through each of the vessels with a pressure gradient along each vessel that is inversely related to the fourth power of the radius. The liquid will also flow at a *mean linear velocity* (distance / unit time) which in each vessel will be proportional to flow (V) and inversely proportional to its *cross-sectional area (ðr^2).* Thus velocity = V / ðr^2 and the narrower the vessel, the smaller the cross-sectional area and the faster the velocity.

In a parallel arrangement the pressure gradient across each of the parallel vessels will be the same and the flow through each vessel will be directly proportional to the fourth power of the radius. If the parallel vessels constitute an increase in total cross-sectional area, the total mean linear velocity through them will be slower. Since the flow through each parallel vessel is different, the velocity in each is derived by substituting from the Hagen-Poiseuille equation for V in the last equation. Thus velocity = deltaPr^2 / 8çl and in each individual parallel vessel velocity will be directly proportional to the square of its radius. In capillaries, extensive branching resulting in a large total cross-sectional area ensures that their combined resistance, the pressure gradient along them and individual velocities within them are small.

A moving liquid because of its mass has *kinetic energy,* which is proportional to the density of the liquid and the square of the mean linear velocity. As described by *Bernoulli's equation,* the total energy in a moving liqyud is the sum of the kinetic energy and the *potential energy.* The latter is the hydrostatic pressure at any point along the length of the horizontal vessel. If the liquid flows suddenly from a narrower vessel into a much wider vessel, there will be a large decrease in velocity and hence in kinetic energy. However, as there will be little change in total energy, there is a relative increase in the hydrostatic pressure in the wider vessel. This becomes important in the cardiovascular system whenever there is a pathological bulge in an artery.

Deviations of Blood Flow from that Predicted

The Hagen-Poiseuille equation was formulated for (i) laminar flow of (ii) a homogenous fluid with constant viscosity through (iii) a rigid unbranched tube. By and large these characteristics do not apply to the vascular system.

Flow, especially in the arteries, is not always laminar. Flow is *pulsatile* in the arteries because of the rhythmic activity of the heart and this will result in a flat rather than a parabolic velocity profile and a lower mean velocity. Furthermore under certain conditions flow can become *turbulent*. This is characterized by eddies of liquid particles moving not only parallel to the vascular axis but also perpendicular to it, and this flattens the velocity profile. The increased internal friction results in volume flow becoming proportional to the square root of the pressure gradient. In other words to double turbulent volume flow requires a quadrupling of the pressure gradient. Turbulence always occur transiently in the aorta or pulmonary artery during early systole and it can occur in large arteries if velocity is high and excedes a critical value (i.e. in severe exercise). If viscosity is low (i.e. in severe anaemia) or there are pathological irregularities of the inner wall (sclerosis) turbulence occurs at a lower critical velocity. The nosie of turbulent flow can be heard with a stethoscope.

Blood is not a homogeneous liquid with a constant viscosity inasmuch as it comprises cells and plasma. The former are responsible for most of the blood's viscosity. A greater proportion of the blood cells travel in the central or axial stream of flow resulting in a greater proportion of the less viscous plasma near the wall of the vessel. This flattens the parabolic velocity profile. Axial streaming is more evident as velocity increases. Thus the *effective viscosity* is less at high velocities and greater at low velocities. Under pathological conditions, low velocities can occur even in large vessels, either as a result of failing heart or in a vessel distal to a pathological constriction. This results in aggregation of erythrocytes into rouleaux causing large increases in effective viscosity which will reduce the velocity still further. Since blood flows through capillaries at a low velocity, the effective viscosity would be expected to be high. However this does not occur because of an unexplained phenomenon in which the effective viscosity of any fluid suspension decreases considerably with decreasing tube radius as it flows through tubes smaller than 100 microm in radius. The effective viscosity of blood flowing through capillaries is also decreased because the erythrocytes travel trhough in single file, a phenomen referred to as *'plug flow'*. Furthermore in capillaries the effective viscosity of blood depends on the *deformability* of erythrocytes since they are larger than the capillaries they traverse. In sickle-cell anaemia the desaturated haemoglobin is crystalline and this reduces considerably erythrocyte deformability.

Total blood viscosity increase when there is an increase in the number of red blood cells (increased haematocrit) as occurs, for example, in response to altitude. Such an increased viscosity will require more work from the heart to generate a greater pressure to maintain normal blood flow. Total blood viscosity decreases during anaemia.

Blood vessels are not rigid but elastic tubes which, during the increased pressure gradient that accompanies increased blood flow, are *passively stretched* to varying degrees. This is most marked in systemic veins and in all pulmonary vessels. This passive increase in radius allows a disproportionate increase in blood flow as pressure increases. However smooth muscle in the walls of most systemic arterioles exhibits, without nervously-mediated stimulation, spontaneous contractile activity, giving the wall a background tension called *myogenic tone.* When these arterioles are passively stretched slightly by an increased pressure gradien, their smooth muscle contracts causing constriction of the vessel. This reduction in radius in some arterioles can exactly match the increase in the pressure gradient such that there is no change in blood flow over a certain range of pressure. This is referred to as *myogenic autoregulation* of blood flow.

These passive and myogenic changes in radius that cause flow and pressure relationships to deviate from the predictions of the Hagen-Poiseuille equation must not be confused with the reflex autonomic nervous control of smooth muscle in systemic arterioles. This increases or decreases the radius altering flow accordingly. Therefore in most vascular beds, for a particular arteriolar radius, flow is relatively linearly related to the pressure gradient.

In small blood vessels, in particular, systemic arterioles, the pressure-flow curves do not pass through the origin but intersect at a positive pressure (normally about 20 mmHg for an arteriole) called the *critical closing pressure* below which flow ceases. The explanation for this phenomenon is unknown. The greater the smooth muscle tone the higher is this critical closing pressure. Under pathological conditions, the pressure generated by the heart may not exceed the critical closing pressure of a vessel and, furthermore, concurrent constriction of the arterioles may actually increase the critical closing pressure, making the situation worse.

Other Properties of Walls of Blood Vessels

All blood vessels are lined by an endothelial layer and in addition, except in capillaries, there are varying amounts of elastin, collagen and smooth muscle. The first component allows the vessel to stretch and the latter two tend to limit the stretch. This can be examined by taking an isolated segment of a blood vessel tied at both ends and determining the luminal pressure generated at various volumes. As elastin is stretched it exerts *elastic tension* and the more elastin (for example, in an artery) the greater the luminal pressure generated for a given degree of stretch. Thus an artery has a high *elastic coefficient* (deltaP / deltaV) and a moderate *distensibility* or *compliance* (deltaV / deltaP). With aging, the major arteries become infiltrated with fibrous tissue and therefore less distensible.

Veins have only a small amount of elastin and hence in the volume range where the vein wall is actually being stretched it is less compliant than an artery. However below this range the vein is very distensible because the cross-sectional profile changes from the flattened ellipse of low volumes to the circular shape of higher volumes. This high distensibility explains why veins are often said to have a

high *capacitance* for volume. The compliance of veins is decreased by sympathetic activity.

Systemic and pulmonary arteries are about ten- and two-fold respectively less distensible than systemic and pulmonary veins. Arterioles and capillaries with little or no elastin have low distensibilities. They are therefore relatively rigid.

Strictly speaking, one should consider the *transmural pressure,* P_t, (i.e. the pressure on the inside minus the pressure on the outside of the wall) rather than the luminal pressure. Were the tube rigid the transmural pressure would be irrelevant but an elastic tube will distend if the inside pressure is higher or collapse if the outside pressure is higher. The outside pressure is the hydrostatic pressure of the interstitium and is usually close to zero. Thus the transmural pressure alters the radius of the tube and this affects the *passive wall tension*, T, as described by the *law of Laplace.* For hollow cylinders as opposed to spherical organs like the heart, the other radius of curvature can be ignored since it is infinite for a cylinder and

$$\mathbf{T = P_t r / u \text{ or } P_t = Tu /r.}$$

The tension per unit area of the wall depend on the amounts of elastin, collagen and smooth muscle. These and the resulting tension are appropriate for the radius and wall thickness of the vessel and for the transmural pressure to which the vessel is usually subjected. Note that a similar sized artery and vein have a fairly similar wall thickness but, since the vein is exposed to less transmural pressure, it has to develop less passive tension and appropriately has less elastin than an artery. The thin endothelial cell wall of a capillary has to withstand a much larger transmural pressure than a vein but its very small radius ensures that only a tiny wall tension is required.

If a particular vessel is subjected to an increase in transmural pressure, its distensibility will result in an increase in the radius and a decrease in the thickness leading to large increases in wall tension. The stretched elastin, collagen and smooth muscle can generate these increased passive tensions within the physiological range of transmural pressures. However, an area of the aortic wall may weaken (for example, in severe arteriosclerotic disease) and become more distensible, resulting in a bulge or aneurysm. The increasing radius and progressive thinning of this bulge will require higher tensions (law of Laplace) from an already weakened wall. Furthermore the slower velocity of flow at this point will result in a greater lateral pressure. Thus a point of supture may be reached.

In arterioles and smaller veins, which possess sufficient smooth muscle for their contraction to decrease the radius of the vessel, the reduction in radius and increase in wall thickness will reduce passive wall tension (law of Laplace). Thus the active tension generated by contraction of the smooth muscle will not elevate the total tension as much as expected and the resultant effect of raising transmural pressure will be dampened.

Relationships Between Flow, Pressure, Resistance, Cross-Sectional Area and Volume Throughout the Vascular System

The relationships of these variables have been considered for series and parallel arrangements of vessels and will now be applied to the vascular system. The *parallel branching* of the blood vessels is such that there is a rise in the *cross-sectional area*, greatest in the capillaries and of moderate proportions in the venules and small veins. The *percentage of total blood volume* that is accommodated in each set of vessels is determined by the cross-sectional area and the *length* of individual vessels. Total blood volume is about 5-6 and 4-5 litres respectively in average men and women. In the supine position at rest, about 75% of the blood is in the systemic circuit, about 8% in the heart and about 16% in the pulmonary circuit. The volume in the heart and pulmonary circuit is referred to as the *central blood volume.* The aorta and systemic arteries contain about 12% of the total blood volume with only about 3% in the systemic arterioles and about 6% in the systemic capillaries for, despite their large cross-sectional area, there are nevertheless very short. Most of the blood (about 55%) is accommodated in the systemic venous system indicating its importance as a *blood reservoir.* In the pulmonary circuit about 5% of the total blood volume is in the arterial system.

During standing at rest, the cross-sectional areas are slightly different and about 6% of the total blood volume is in the heart and aboud 9% in the pulmonary circuit, resulting in an increase to about 65% in the systemic venous system. During exercise there will be a greater proportion of blood in systemic capillaries, venules and, to a lesser extent, arterioles (the increase being in the blood supply of skeletal musculature), as well as in the heart and in the pulmonary circuit. The proportion in the systemic venous system will be reduced correspondingly.

The *velocity* in a particular vessel will be the volume flow rate divided by the cross-sectional area. Flow is *pulsatile* in the aorta and arteries and hence velocity changes but the mean velocity is about 20 cm / sec at rest. Flow becomes *non-pulsatile* and very slow at a velocity of about 0.05 cm / sec in the capillaries. This low velocity is vital in that it allows time for adequaye diffusion between blood and the cells across the capillary wall. Since large veins have a cross-sectional area about twice that of the aorta the mean velocity increases to only 10 cm / sec. During exercise increases in cardiac output can cause up to five-fold increases in velocity in the arteries and veins but in the capillaries of skeletal musculature a concommitant increase in cross-sectional area results in very little increase in velocity.

Blood pressure is pulsatile in the aorta and arteries, having in the systemic circuit at rest a systolic peak of about 120 mmHg and a diastolic through of about 80 mmHg. Since the pressure depends upon the volume flow and resistance (Poiseuille's equation), the drop in mean blood pressure along each set of vessels will indicate their relative *resistance.* The larger radii of the aorta and arteries provide very little resistance and the mean pressure along them drops from 100 to only 95 mmHg. As the arteries get smaller the pressure drop becomes bigger (from 95 to 75 mmHg) and these is a progressive transition from pulsatile to non-pulsatile pressure. The greatest

resistance and hence the largest fall in pressure (from 75 to 35 mmHg) occurs along the arterioles. Despite the even smaller radius of the capillaries, their total resistance is only about half that of the arterioles and thus the pressure drop is smaller (from 35 to 15 mmHg). The relatively smaller total resistance of the capillaries is a result of their vast parallel network. The pressure fall allong the venous system is small (15 to 1 or 2 mmHg) because, although veins and arteries are of a similar size, the veins are more numerous and arranged in parallel. In the large veins the blood pressure and hence flow and velocity becomes slightly pulsatile from the action of the right atrium and the nearby arterial pulsations.

In the systemic circuit at rest, therefore, the aorta and arteries constitute about 20%, the arterioles about 50%, the capillaries about 20% and the venous system about 10% of the total resistance to flow. The combined resistance of the parallel vascular beds of the systemic circuit is termed the *total peripheral resistance.* At rest with a total pressure gradient of about 100 mmHg and a cardiac output of 6 L/min, this resistance amounts to about 17 mmHg/Lmin. In the pulmonary circuit, by comparison, with a total pressure gradient of about 10 mmHg there is a *pulmonary resistance* of about 1.7 mmHg/Lmin.

During exercise the profiles will change because the increased force of ventricular contraction and the consequent increase in cardiac output will elevate the mean arterial blood pressure. There is also an increase in the radius of arterioles supplying skeletal musculature. This increase dominates the systemic response resulting in a decrease in total systemic arteriolar resistance and hence a smaller drop in pressure along the arterioles. This will elevate pressures in the capillaries and venous system.

Characteristics of the Systemic Arterial Circulation

Since the blood enters the aorta from the heart only during systole, flow tends to be turbulent and the aortic and arterial blood pressures are pulsatile. Although two-thirds of the stroke volume is ejected during the first third of systole which results in aortic flow and velocity reaching a peak early in systole, the peak of the blood pressure pulse occurs later. This delayed peak in pressure is because the aorta is not a rigid tube and the pressure pulse is modified by the elastic stretching of the aorta. The aorta stretches in systole to accommodate about 50% of the stroke volume whilst the other 50% flows on into the peripheral blood vessels. As the elastin of the aorta stretches the kinetic energy of liquid motion is converted into potential energy. In diastole, as the elastic recoil converts potential energy back to kinetic energy, the aortic pressure does not drop to zero but falls gradually to a minimum of about 80 mmHg. This relatively high pressure during diastole ensures that the blood accommodated in systole is propelled out to the periphery during diastole. The pulsatile blood propulsion from aort to the periphery results from the sequence of expansion followed by recoil of the next section of the aorta and later of the arteries. This elastic recoil converts the intermittent flow from the heart into a continuous, albeit pulsatile, flow through the arterial system.

The *pressure pulse* is transmitted through the arteries with a velocity considerably greater than the forward movement of blood itself (the flow pulse). The latter has a mean velocity of about 20 cm/sec in the aorta and about 15 cm/sec in a small artery. In comparison the pressure pulse has a very high velocity of about 4 m/sec in the aorta reaching about 12 m/sec in small arteries. This pressure pulse (pulse-wave) is transmitted through the column of blood and along the vessel walls and its velocity is higher the less viscous the blood, the greater the mean blood pressure, the more rigid or thicker the vessel wall and the smaller the lumen radius. With increasing age the greater wall stiffness results in an increased pusle-wave velocity as does the overstretching of arterial walls in hypertension.

Because branching increases the arterial cross-sectional area, the amplitude and velocity of the pulses in arterial flow decrease at increasing distances from the heart. In contrast to the flow pulse the amplitude of the pressure pulse increases. The diastolic pressure decreases as a result of the pulse-wave losing energy from the alternating transfer between kinetic and potential energy. Although the mean pressure falls continuously, the systolic pressure increases as a result of complex fluid dynamics which include the reflection of energy back towards the heart because of the decreased distensibility of the smaller arteries. Such factors also dampen the sharp vibration of the incisure seen in the aorta and convert it to the smaller *dicrotic notch* and the distinct *dicrotic wave* of the artery.

Clinically these arterial pressure pulses can be felt, giving information not only about heart rate and its regularity but also about increased stroke volume or decreased distensibility. The tension or hardness of the pulse reflects the mean arterial blood pressure. Electromechanical transducers placed on the skin over an artery yield details about the shape or contour of the pulse and provide more precise clinical information.

Measurement of Arterial Blood Pressure

The maximum of the pressure pulse is called the *systolic blood pressure* (at rest the range is 100-140 mmHg at 20 years of age) and the minimum is the *diastolic blood pressure* (range 50-90 mmHg). With increasing age systolic, in particular, and diastolic pressure increase due to loss of arterial elasticity. The difference between systolic and diastolic pressure is the *pulse pressure.* The *mean arterial pressure,* which is the driving force for blood flow, is determined by integrating the pressure pulse against time. Different pressure pulse contours in the arterial system mean that for the aorta the mean arterial pressure (about 100 mmHg) is approximately the arithmetic mean of the systolic and diastolic pressure or, expressed another way, the diastolic pressure plus half the pulse pressure, whereas in a peripheral artery it is approximately the diastolic pressure plus one third of the pulse pressure (about 95 mmHg).

These pressures can be measured directly by inserting a fluid-filled cannula into the appropriate artery and recording with an electrical pressure transducer. Clinically they are measured indirectly by a *sphygmomanometer*. This comprises an inflatable rubber cuff covered by a layer of non-distensible fabric which is usually wrapped around the upper arm at the level of the heart and attached to a mercury

manometer. The cuff pressure is altered by pumping air into the cuff or releasing it through a needle valve. A stethoscope is placed distal to the cuff over the brachial artery in the elbow. The cuff is then inflated to a pressure higher than the expected systolic pressure compressing the blood vessel so that no blood flows through the artery. When the cuff pressure is slowly released, varying sounds (*Korotkoff sounds*) detectable with the stethoscope result from the intermittent and turbulent flow of blood through varying degrees of constriction of the brachial artery. Four phases of sound followed by a phase V of silence can be distinguished.

When the cuff pressure has fallen to just below the systolic pressure, a clear, but often faint, tapping sound suddenly appears in phase with each cardiac contraction. The tapping sound is produced by the transient and turbulent blood flow through the artery during the peak of each systole. The systolic pressure is defined as that cuff pressure at which the tapping sound is suddenly heard. During the next 15 mmHg fall in the cuff pressure, the tapping sound becomes louder (phase I). In the following 20 mmHg fall, the sound becomes quiter with a murmuring quality (phase II) and may suddenly disappear in the latter part of this phase (the auscultatory gap). In the next 5 mmHg fall in cuff pressure, the sound of the murmuring becomes very loud and thumping (phase III). In the following 5 mmHg fall the sound becomes muffled and rapidly grows fainter (phase IV) and finally the sound disappears (phase V). When blood flow velocity is high, for example in exercise, the beginning of phase IV and V may be separated by 40 mmHg or more. The beginning of phase IV (muffling) and of phase V (disappearance) are used to measure diastolic pressure. The diastolic pressure is usually defined as the cuff pressure at which muffling not disappearance occurs. However, if there is an obvious difference at rest between these, both values are reported.

Determinants of Arterial Blood Pressure

The relative importance of any single factor in determining the arterial blood pressure is most simply examined if all other factors are held constant. In general, systolic pressure is affected mainly by stroke volume and in particular by ejection velocity, and diastolic pressure by total peripheral resistance and the time allowed for blood to flow out of the arteries (i.e. the duration of diastole which is determined by the heart rate). In greater detail systolic pressure is increased by (i) an increase in the diastolic pressure of the previous pulse, (ii) an increase in stroke volume, (iii) an increase in ejection velocity (without a change in stroke volume), or (iv) a decrease in aortic or arterial distensibility. Diastolic pressure is increased by (i) an increase in the systolic pressure of that particular pulse, (ii) a decrease in ejection velocity, (iii) an increase in aortic or arterial distensibility, (iv) an increase in heart rate or (v) an increase in total peripheral resistance. The resultant changes in pulse pressure and mean arterial pressure will depend on the direction and relative magnitude of the individual changes in systolic and diastolic pressures.

The numerical values given above for arterial blood pressure (and pressures elsewhere in a vascular system) are for the supine position when the vessels are at the level of the heart. In the vertical position the pressures are affected by gravity.

Circulation Through the Arterioles and the Regulation of Blood Flow in the Systemic Circuit

Since arterioles constitute at rest about 50% of the total peripheral resistance, they are the site of the largest fall in the blood pressure and are also the site at which the resistance is altered. Contraction of the smooth muscle in the wall of the arteriole (*vasoconstriction*) decreases its radius thereby increasing its resistance, so that there is a larger fall in blood pressure along the arteriole and a decrease in blood flow through it. The converse follows relaxation of the smooth muscle (*vasodilatation*). At rest, the degree of vasoconstriction of the arterioles to a particular organ relative to other organs will regulate the proportion of the cardiac output that it receives.

Smooth muscle is arranged around the circumference of arterioles. One type (*myogenic*) can contract spontaneously. The other type requires innervation by the *sympathetic system* in order to contract. At rest there is a tonic discharge in these sympathetic nerves, which together with any myogenic contraction and that caused by circulating humoral agents, gives a background degree of vasoconstriction referred to as *vasomotor tone.* Its degree varies from organ to organ. For example, at rest it is high in arterioles of the skeletal musculature and low in those of the gut, kidney and skin. The higher the vasomotor tone at rest, the greater the increase in blood flow during maximal vasodilatation.

Intrinsic Regulation of Blood Flow

1. In the brain and kidney the smooth muscle of the arterioles spontaneously contracts when the pressure increases and relaxes when the pressure decreases, which allows a blood flow that is independent of variations in arterial blood pressure. This *myogenic autoregulation* is less well developed, or overriden by other mechanisms, in the heart, gut and skeletal musculature. It does not occur in the skin.

2. All organs need to increase their blood flow in proportion to their metabolic requirements. During increased metabolism there is a decrease in the partial pressure of O_2 , an increase in the partial pressure of CO_2 and an increase in H+ concentration in the interstitial fluid. These changes cause the smooth muscle to relax to a degree that is appropriate to the increased metabolism. This is called *metabolic autoregulation.* Increases in local temperature and in the local concentrations of other metabolites such as ATP, ADP, AMP, adenosine, lactate and pyruvate, as well as increases in the K+ concentration and interstitial osmolarity of exercising skeletal musculature, have been said to cause vasodilatation. Metabolic autoregulation is well developed in the skeletal musculature, heart, brain, but in other organs it can be overriden by nervous control of the arterioles. It may contribute to the phenomenon of myogenic autoregulation inasmuch as an increase in pressure by increasing blood flow, in the face of constant metabolism, will lower tissue metabolites and result in vasoconstriction.

Small changes in the metabolism of an organ can be satisfied by metabolic autoregulation without affecting significantly the total peripheral resistance. However

the metabolism of an organ may increase so markedly that there will be a fall in total peripheral resistance. The resultant initial fall in mean arterial blood pressure will then elicit cardiovascular nervous reflexes to increase cardiac output and restrict the blood flow to other organs in order to maintain the mean arterial blood pressure.

When the blood supply to an organ is temporarily obstructed (for a period of seconds up to a few minutes), its restoration is accompanied by a large increase in blood flow (*reactive hyperaemia*) which depends on the duration of the obstruction and the metabolism of the organ over that time. The vasodilatating effects of the metabolites that have accumulated during the obstruction contribute to this reactive hyperaemia.

An increased P_{CO2} (hypercapnia) or a decreased P_{O2} (hypoxia) in arterial blood will cause vasodilatation of all systemic arterioles. However hypercapnia and hypoxia, especially the former, will also elicit cardiovascular reflexes which oppose this vasodilatation.

3. In addition to metabolites, other chemicals released locally in an organ also affect its blood flow - *humoral control.* The salivary, gut and sweat glands when activated produce not only their exocrine secretions but also an enzyme kallikrein. This converts plasma kininogens into active *kinins*, such as *kallidin* and *bradykinin*, which have marked vasodilating effects on the gland as well as locally within the skin or gut. These kinins are inactivated by other tissue enzymes. Kinins are also liberated in all other tissues during inflammatory and allergic responses. In response to tissue damage or allergic responses, the vasodilator, *histamine* is released from granulocytes and mast cells and when a blood vessel is cut the vasoconstrictor substance, *serotonin*, is released from the platelets. Some *prostaglandins* are vasoconstrictors, others are vasodilators, but the physiologic role of these effects remain to be clarified.

Extrinsic Regulation of Blood Flow

1. *Nervous control.* Since there is a resting vasomotor tone, an increase in *sympathetic discharge* to the arterioles causes further vasoconstriction whilst a decrease in discharge causes *vasodilatation.* The sympathetic neurotransmitter, *noradrenaline*, acts powerfully on *alpha adrenergic receptors* on the plasma membranes of vascular smooth muscles to cause contraction. Noradrenaline also acts weakly on the beta2 adrenergic receptors of vascular smooth muscle, the activation of which causes relaxation. However, the strong alpha response is dominant. Arterioles of the skin, gut, skeletal musculature and kidneys receive a dense sympathetic innervation whereas those of the brain, and to some extent of the heart, are sparsely innervated. This indicates that there is little nervous control of the circulation to these latter organs.

The vasoconstriction resulting from a certain level of sympathetic discharge is considerably greater in the skin, kidney and gut than in the skeletal musculature. Thus the blood flow to the skin, kidney and gut can be restricted in favour of other organs. This sympathetic pathway is controlled by the cardiovascular centres in the

medulla oblongata and pons and operates, for instance, during the baroreceptor reflex to maintain mean arterial pressure.

A special system of sympathetic nerves controlled from the motor cortex and hypothalamus innervates the arterioles of the skeletal musculature. It releases acetylcholine at the postganglionic nerve ending and causes vasodilatation. This *sympathetic cholinergic pathway* is usually silent but is activated during emotional reactions of alarm, rage or fear during the initial phases of exercise.

The external genitalia receive a vasodilatating *parasympathetic* and a vasoconstricting sympathetic innervation and this dual innervation is integrated in the spinal cord. Parasympathetic nerves to the arterioles of the brain, heart and lung exist but their functional significance is not clear.

2. *Hormonal control.* The adrenal medulla continuously secretes *adrenaline* and a small amount of noradrenaline. The level of secretion is proportional to its sympathetic discharge which is under the control of hypothalamus. Adrenaline activates to an equal extent the *alpha adrenergic receptors* resulting in vasoconstriction and the *beta2 adrenergic receptors* resulting in vasodilatation. The net arteriolar response of a particular organ to adrenaline depends on the relative densities of alpha and beta2 receptors. The density of beta2 receptors is higher in skeletal musculature and the heart. Thus during exercise the increased release of adrenaline contributes to the increased blood flow to the skeletal musculature and the heart whilst decreasing the blood flow to the skin, gut and kidney.

The hormones angiotensin II and antidiuretic hormone (vasopressin) also cause vasosonstriction, in particular the former. However these hormones are involved in the control of blood volume rather than blood flow.

Circulation Through the Capillaries

The entrances from the arterioles (or metarterioles) into the vast network of capillaries are guarded by a ring of smooth muscle, the *precapillary sphincter.* These sphincters exhibit *myogenic rhythmicity* which results in intermittent and variable flow rates through any individual capillary. The direction of the flow may change in some capillaries depending on both their location within the capillary bed and the degree of constriction of nearby sphincters. The net degree of constriction or dilatation of these sphinctera is controlled by *metabolic autoregulation*. For example, in skeletal musculature at rest, at any one moment about 10% of the capillaries are 'open' and the rest contain blood that is stationary or they may even be completely empty. Blood bypasses the capillaries and flows through the *metarterioles* which contain little smooth muscle and through special capillaries called *throughfare channels.* In the skin and gut short, relatively large diameter vessels called *arteriovenous anastomoses* act as shunts between arterioles and venules. They have thick walls of smooth muscle controlled by sympathetic nerves acting on alpha adrenergic receptors. Note that the capillaries themselves are not contractile nor are they distensible.

The parallel arrangement of the narrow (4 microm radius) capillaries, their contribution (20%) to the resting total peripheral resistance, the blood pressure drop along them, the absence of pulsatile flow, their large cross-sectional area, the low velocity of flow in the capillary bed and the low flow rate through an individual capillary have already been described. Under resting conditions only about 25% of the capillaries are open giving a cross-sectional area of about 3000 cm^3. Since the average length of a capillary is about 0.1 cm and the velocity of blood flow is 0.05 cm/sec, blood will take about 2 sec to traverse a capillary at reat. When a tissue increases its metabolic rate, more of its capillaries are open, increasing its capillary cross-sectional area but, since vasodilatation of the supplying arteriole will increase the blood flow to the tissue, the velocity through the capillary may increase. The *transit time* through the capillary is rarely faster than 1 sec, which is still sufficient to allow complete equilibrium by *diffusion* of gases and nutrients across the wall of the capillary. The vast network of the capillaries also provides a *large surface area* for exchange, with a *short diffusion distance* of about 50 microm between blood and cells. The area increases and the distance decreases whenever the number of open capillaries increases.

Ultrafiltration and Reabsorption of Fluid Across the Capillary Wall

At rest the difference in hydrostatic pressure between the capillary blood and the interstitial fluid, which favours ultrafiltration of fluid from the capillary into the interstitial fluid, is virtually counterbalanced by colloid osmotic forces which favour the return of fluid to the capillary (the *Starling equilibrium*). Any small amount of fluid lost into the interstitium is removed by the *lymphatic system.* In a variety of circumstances this equilibrium may be disturbed, resulting in fluctuations in the circulating *blood volume.*

Excess ultrafiltration will occur with (i) arteriolar vasodilatation, ii) an elevated arterial pressure (i.e. hypertension), (iii) an elevated venous blood pressure (i.e. in the erect posture or in cardiac failure), (iv) decreases in plasma osmotic pressure (plasma protein deficiency) and (v) increases in interstitial protein concentration (inadequate lymph drainage or the action of histamine and kinins which increase the protein permability of the capillary). However excessive increases in the volume of the interstitial fluid (*oedema*) are usually limited by factors that will increase lymphatic flow.

An excess of reabsorption will result mainly from (i) arteriolar vasoconstriction, (ii) a decreased venous blood pressure and (iii) dehydration which will increase plasma protein concentration. In haemorrhage, increases in fluid reabsorption will occur indirectly as a response to the lowered capillary blood pressure and directly as a reflex response to haemorrhage via the vasoconstriction induced by increased sympathetic activity and increased circulating angiotension II. Such responses will help to restore the blood volume by drawing on the reservoir of the extracellular fluid in the interstitium, principally from the skeletal musculature.

Characteristics of the Systemic Venouc Circulation

The following characteristics have already been described viz., the cross-sectional area of the systemic venous system in comparison with arteries and capillaries, the fact that the veins accommodate 55% of the blood volume when supine, the moderate venous velocity, the venous contribution of 10% to the total peripheral resistance, the resulting small pressure gradient (from 15 to 1 or 2 mmHg) and, in the largest veins, the slightly pulsatile nature of venous flow (a, c and v waves). Two important characteristics of the venous system which require further discussion are the venous pressure gradient, which will determine *venous return* to the right atrium, and the venous distensibility which influences the *venous capacity* for accommodating blood volume which also affects venous return.

Alterations in Venous Capacity

The distensibility of the venous system allows increases or decreases in total blood volume to be accommodated passively with little detectable increase or decrease in venous pressure. It also means that increased or decreased transmural pressure will result in the passive distension or compression of the veins.

Smooth muscle iun the walls of the venous system is relatively sparse, except in the splanchnic and cutaneous circulation, has *alpha adrenergic* receptors and is innervated by the *sympathetic system*. There is normally some degree of tonic discharge and hence some degree of constriction, *venomotor tone.* An increase in sympathetic activity or in circulating adrenaline and angiotensin II will cause *venoconstriction.* This reduces the capacity of the venous system and makes its walls less distensible. Because of the relatively large radii in the venous system, venoconstriction has little effect on venous resistance or total peripheral resistance. Conversely, a decrease in sympathetic activity to the veins results in *venodilatation* and an increase in venous capacity. Venoconstriction occurs as part of the reflexes coordinated by the cardiovascular centres in response to haemorrhage or during exercise.

Determinants of Venous Return

The pressure gradient through the venous system is the primary determinant of venous return. This pressure gradient is the difference between *mean systemic filling pressure (MSFP)* and *mean right atrial pressure.*

The MSFP was defined by Guyton in the 1950s as the weighted average of the pressures in all portions of the systemic circulation. The weighting is in proportion to the volume capacity of the vessel. It is also the static blood pressure which prevails throughout the systemic circulation if the heart is suddenly arrested experimentally and rapid equilibrium of pressures in arterial and venous circuits has occurred. The MSFP is usually about 7 mmHg. In the dynamic situation, this pressure is reached in about the middle of the systemic venous circuit and thus the MSFP is approximately equal to the *mean venous pressure.* The MSFP is increased by an increase in total blood volume and by an increase in venomotor tone which reduces

venous compliance and venous capacity. Although arteriolar vasoconstriction will decrease capillary and venous pressures, reduce cardiac output and hence venous return, it will not alter MSFP. The maximum MSFP is about 20 mmHg and the minimum MSFP can be close to zero.

The mean pressure in the right atrium, often referred to as *central venous pressure,* is about 1 mmHg. It is elevated slightly in the supine position compared with the standing position and when total blood volume is increased. It can be elevated appreciably during right heart failure.

Secondary factors also influence venous return. Because the right atrial pressure fluctuates in phase with the heart rate, this reults in fluctuations in venous return. The increase in atrial pressure during atrial contraction reduces venous return whilst both the downward movement of the atrioventricular ring during early systole and the rapid filling of the ventricle after the AV valve opens during early diastole decrease the atrial pressure, often to negative values, and hence increase venous return. This so-called *'suction effect of the heart'* therefore aids venous return and is greater during increased cardiac activity.

Since the atria are influenced by the subatmospheric pressure of the thorax (the intrathoracic or intrapleural pressure) which at rest is about -3 mmHg during expiration and about -5 mmHg during inspiration, there is a further fluctuation in atrial pressure that is synchronous with respiration. Thus during inspiration atrial pressure decreases and causes a greater systemic venous return to the right atrium. Such an effect of increasing pulmonary venous return to the left atrium is opposed by the intrapleural pressure of inspiration causing a passive dilatation of pulmonary blood vessels. This increases the capacity of the pulmonary vessels and hence transiently during inspiration decreases venous return to the left atrium. The converse changes happen during expiration. This explains the respiratory-induced changes in preload to the right and left ventricles and hence in their stroke volumes.

Venous return is also assisted by the effect of intrapleural and abodminal pressures on the intrathoracic and intra-abdominal veins respectively, the so-called *respiratory venous pump.* Since veins have distensible walls, the fluctuations in transmural pressure in the thorax cause dilatation of intrathoracic veins during inspiration and their compression during expiration. The descent of the diaphragm during inspiration will, at the same time, raise intra-abdominal pressure and compress the abdominal veins. The converse will occur in expiration. Thus the respiratory pump, within limits, aids venous return since the relative dilatation of intrathoracic veins in inspiration will decrease their resistance to flow and cause some movement of blood towards the heart from the abdominal veins or upper extremities. The simultaneous compression of abdominal veins propels blood towards the heart since retrograde flow from the abdomen into the limbs is prevented by valves in the limb veins. *Venous valves* are thin cup-like structures whose cusps obstruct the lumen at the threat of any retrograde flow and thus ensure unidirectional flow. They occur only in veins of the limbs. In expiration relative dilatation of the abdominal veins causes some movement of blood into the abdomen from the lower limbs. Whenever

the depth of breathing increases, for instance during exercise, the effects of the respiratory pump on venous return is enhanced.

During exercise a further mechanism, the *skeletal muscle venous pump,* aids venous return. The exercise must not be a sustained contraction but one of alternating contraction and relaxation. The contraction of the skeletal musculature alters the transmural pressure compressing the veins within it. This propels blood towards the heart since retrogradew flow is prevented by the venous valves. When the skeletal musculature relaxes, the veins are dilated by inflow but only from below since the venous valves prevent retrograde flow.

Relationships Between Cardiac Output, Venous Return and Atrial Pressure

The separate considerations of the control of cardiac output (in particular stroke volume) and of venous return can now be combined in a graphical approach designed by Guyton in the 1950s. It must be noted that these graphs represent only steady-state responses and not momentary changes and that the use of them requires some simplification of concepts and abstraction of ideas.

Earlier, the relationship between stroke volume and end-diastolic volume (the Starling curve) was described together with the concept that they could be considered as similar to cardiac output and mean atrial pressure respectively. This relationship is referred to as the *cardiac* or *ventricular function curve.* The position of function (normally at a) moves up the curve when venous return increases since this results in a higher mean atrial pressure and hence a larger end-diastolic volume. Conversely the position of function moves down the curve when venous return decreases. The curve becomes steeper during increased sympathetic stimulation of the ventricle (i.e. an increase in myocardial contractility) or during a decreased afterload in the arterial system (i.e. vasodilatation). A flatter curve occurs during the converse conditions or during ventricular failure or disease of the heart valves.

The equivalent relationship between venous return and mean atrial pressure is referred to as the *systemic vascular function curve.* As atrial pressure is increases venous return is opposed whilst there is a limit to the possible increase in venous return caused by negative atrial pressures because they will also result in a tendency for collapse of the venae cavae in the chest. At a venous return of zero the atrial pressure in this graph is + 7 mmHg, that is, the pressure (*mean systemic filling pressure, MSFP*) throughout the cardivascular system when the circulation has been stopped experimentally long enough for the pressure to have equalized. The systemic vascular function curve shifts upwards in a parallel manner whenever there is an increase in blood volume or during venoconstriction. This indicates an increase in MSFP. The converse occurs during a haemorrhage or venodilatation. A decrease in total peripheral resistance (vasodilatation) causes a steeper curve but does not alter the MSFP. Vasoconstriction flattens the curve.

When the ventricular and systemic vascular function curves are displayed together the position of function is the point of intersection 11.44c) and at rest in health this is at a. During exercise the increased myocardial contractility would result

in position b. The steepness of this new cardiac function curve would also depend on the degree of vasodilatation. However the venous capacity also decreases during exercise and hence together with the vasodilatation results in an upward shifted systemic vascular function curve such that the actual position of function in exercise is at c.

Characteristics of the Lymphatic System

The lymphatic system constitutes a secondary set of drainage vessels, extending from a vast peripheral network of blind-ending lymph capillaries in the interstitium to large lymph vessels entering the subclavian veins via the right lymphatic duct and on the left via the thoracic duct. It returns to the cardiovascular system *excess interstitial fluid* and any *protein* that has leaked across the capillary wall. It also acts as a pathway for the *absorption of fats* from the gut and, by virtue of its lymph nodes and lymphocytes, is involved in *immune responses.*

Lymph flows sluggishly at a rate of about 2 litres / day. The pressure gradient driving this flow depends on the *interstitial hydrostatic pressure*, the magnitude of which is proportional to the amount of excess interstitial fluid. Lymph flow is aided by the *myogenic* rhythmic contractions of *smooth muscle* in the walls of lymph vessels, retrograde flow being prevented by *lymphatic valves* similar to those found in veins. During exercise the rate of lymph flow can increase up to ten-fold as a result of rhythmic contractions of skeletal musculature around the lymph vessels. Similarly, increased contractions of gut musculature will increase lymphatic return from the intestine. Furthermore rhythmic alterations in the transmural pressure resulting from the cardiac and respiratory cycles will aid lymphatic return from the heart and lungs respectively.

11.4 Integrated Regulation of the Cardiovascular System

The *short-term regulation* of the cardiovascular system is concerned with the immediate adjustment of three variables - cardiac output (Q), total peripheral resistance (TPR) and mean arterial blood pressure (MAP). It operates at all times to maintain a particular steady-state condition. Compensatory changes occur within seconds following perturbations such as a change in posture, haemorrhage or exercise. These compensations are dependent on a variety of sensory receptors, on the integration of the sensory information by the cardiovascular centres in the medulla oblongata and pons, which are also influenced by higher brain centres, and on the autonomic motor pathways to the heart and blood vessels. This autonomic (extrinsic) control interacts with the intrinsic control mechanisms operating within the heart and blood vessels.

The relationship V= deltaP / R, used previously in considering flow through a single vessel, must also apply to the systemic circuit as a whole. Here

Cardiac output = (MAP - MRAP)/TPR.

Since mean right atrial pressure (MRAP) is close to zero, this equation can be condensed to

Q = MAP/TPR.

Both Q and TPR are controlled by a combination of intrinsic and extrinsic mechanisms. The control of Q can be considered in terms of (i) the intrinsic control of stroke volume by the magnitude of the end-diastolic volume (Starling's law of the heart), (ii) the extrinsic control of stroke volume by sympathetic nerve fibres and by adrenaline and (iii) the extrinsic control of heart rate by parasympathetic and sympathetic nerve fibres and by adrenaline. In addition, extrinsic control of venous capacity by sympathetic nerves and passive changes in venous capacity will alter end-diastolic volume and hence influence the intrinsic control of stroke volume. The control of TPR can be considered in terms of intrinsic control by metabolic autoregulation and extrinsic control by sympathetic nerve fibres and adrenaline. There is no direct control of MAP. It is a dependent variable, altered only indirectly by altering Q or TPR or both. In contrast there are no sensory receptors which directly monitor Q or TPR but there are sensory receptors, *arterial baroreceptors,* which directly monitor MAP.

Arterial Baroreceptor Reflexes

Baroreceptors are located in the walls of the aortic arch and in the enlarged part (the *carotid sinus*) of the internal carotid artery just after it arises from the common carotid artery. The unmyelinated and encapsulated nerve endings of the baroreceptors are embedded in the elastic tissue of the arterial wall and are stimulated by stretching of the wall. The sensory myelinated axons from the *aortic baroreceptors* travel in the *vagus nerve* and those from the *carotid baroreceptors* travel in the *glossopharyngeal nerve* to the cardiovascular centres.

The aortic baroreceptors are less sensitive than the carotid baroreceptors. An increase in transmural pressure, usually brought about by an increase in arterial blood pressure, will stretch the arterial wall and stimulate the baroreceptors. At normal MAP, carotid baroreceptors are tonically active as shown by streams of action potentials recorded from their afferent axons. The mean frequency of these action potentials changes in direct proportion to changes in MAP in the blood pressure range of 50 to 180 mmHg. Also the frequency of nervous discharge from the baroreceptors is in phase with the fluctuation from systolic to diastolic arterial pressure. Baroreceptors monitor the sudden increase in MAP that occurs after a change in posture from standing to supine and the sudden decrease in MAP that occurs after a haemorrhage or after a change in posture from supine to standing.

The reflex changes initiated by stimulation of the arterial baroreceptors in response to a sudden increase in MAP are as follows:

(i) an increase in parasympathetic and a decrease in sympathetic discharge to the SA and AV nodes causing a decrease in heart rate;

(ii) a decrease in sympathetic discharge to ventricular muscle causing a decrease in contractility and hence a reduction in stroke volume;

(iii) a decrease in sympathetic discharge to the veins causing an increased venous compliance and capacity and hence a reduced end-diastolic volume and subsequent stroke volume;

(iv) a decrease in sympathetic discharge to the arterioles causing a decrease in TPR. This vasodilatation results in a greater capillary pressure leading to an increased ultrafiltration across the capillary wall and hence, after about 5 min, to some reduction in blood volume.

All these changes except (iv) will reduce Q. Since Q=MAP/TPR, the reflex reductions in Q and TPR will decrease MAP thus opposing the initial elevation and restoring the MAP to or towards normal. A decrease in MAP initiates the converse changes.

The baroreceptor reflexes adjust the balance amongst Q, TPR and MAP whenever there is a small change in the metabolism of an organ. If one organ increases its metabolism, dilatation of its arterioles by local metabolic autoregulation rapidly increases its blood flow. This local vasodilatation will slightly decrease the TPR and hence the MAP. The smallest decrease in MAP will be detected by the baroreceptors and will result in a reflex increase in Q and, to some extend, an increased vasocontriction in other organs, except the heart and brain. Thus, within a few seconds, the final decrease in TPR will be minimized and the extra blood flow required by that organ will be supplied by reducing blood flow to some other organs and by increasing the total blood flow. At the same time the decrease in MAP will be very small or even undetectable.

The precision of the baroreceptor reflex in regulating MAP at 100 mmHg depends on the magnitude of the initial deviation, on the influence of other receptor reflexes and on higher centre control of the cardiovascular centres. These other factors determine the final set-point for the MAP and the role of the baroreceptor reflex is to ensure that any particular set-point is maintained. If the baroreceptors are denervated the MAP is very variable around whatever the set-point, although initially the MAP will also be elevated.

Reflexes Initiated by Cardiac Stretch Receptors

Stretch receptors are also found in the walls of the venae cavae (as they enter the heart), the atria and the ventricles. Their afferent fibres are myelinated, except for those from the ventricles, and they travel in the *vagus nerve* to the cardiovascular centre. A physiological function is only well established for the reflexes resulting from stimulation of atrial and venae cavae receptors. Both are referred to as *atrial 'B' receptors.*

Since increase in blood volume in the atria cause a lot of stretch for only a small increase in the low atrial pressure, these atrial 'B' receptors are low-pressure or

volume receptors. Their peak stimulation occurs during the v wave of atrial pressure at the very end of systole. An increase in blood volume increases the total nervous discharge from the atrial 'B' receptors and reflexly initiates a decrease in sympathetic and an increase in parasympathetic activity. This complements the reflexes initiated by the baroreceptors which will also be stimulated by the increase in MAP that usually accompanies an increase in blood volume. These reflexes together result in a decrease in Q and TPR, an increase in venous capacity and an excess of ultrafiltration across the capillary wall. Thus MAP and blood volume decrease towards normal.

The stimulation of atrial 'B' receptors initiates further reflexes which act over a longer term to correct the underlying disturbance - the increased blood volume. It preferentially reduces the sympathetic to *renal arterioles* and the consequent increase in renal blod flow decreases *renin* released by the kidney and facilitates urinary *sodium excretion.* The decrease in renin reduces the sensation of *thirst* and decreases the circulating concentration of *angiotensin II,* giving further vasodilatation and decreased TPR. The decrease in renin will also decrease the amount of *aldosterone* released from the adrenal cortex which will further enhance urinary sodium excretion. Furthermore, afferent nerves from the atrial 'B' receptors also pass through the cardiovascular centre to the *hypothalamus* and decrease the amount of *antidiuretic hormone* released from the posterior pituitary. Thus water, as well as salt, is lost in the urine. Finally restoration of normal extracellular fluid volume and, in particular, normal blood volume is achieved.

These effects of renin, angiotensin II, aldosterone and antidiuretic hormone take from minutes to hours to develop. Such *long-term regulation* of blood volume and hence of MAP and mean systemic filling pressure involving the endocrine, renal and cardiovascular systems not only compensates for the decreased blood volume of a *haemorrhage* but also operates at all times in the background to maintain *total body water* and the *correct distribution of extracellular fluid* between the interstitium and the blood.

Other cardiac stretch receptors, the physiological functions of which are speculative, are as follows. *Atrial 'A' receptors* are excited normally by atrial contraction (at the time of the a wave) and experimentally by a rapid infusion of a large blood volume. The reflex initiated is an increase in heart rate mediated by the sympathetic system (Bainbridge reflex). In the *left ventricle* stretch receptors stimulated normally by the isovolumetric phase of ventricular contraction result in a decrease in heart rate and vasodilatation. These receptors appear to be stimulated also by alkaloids (i.e. veratrine), serotonin, nicotine and the accumulation of metabolites (Bezold-Jarisch reflex). In the *right ventricle* stretch receptors, the afferents of which travel with sympathetic nerve fibres, may reflexly increase cardiac output and respiration when stretched by the larger end-diastolic volume of exercise.

Reflexes Initiated by Other Receptors

The receptors described below alter the set-point for MAP.

1. *Lung stretch receptors* are stimulated by the increase in tidal volume accompanying an increased ventilation, for example during exercise, and not only determine the pattern of breathing but also cause an increase in heart rate and a decrease in TPR and MAP.

2. *Nasal receptors* when stimulated by water in diving mammals cause a cessation of breathing and a decrease in heart rate and an increase in TPR and MAP (the diving reflex).

3. *Peripheral or arterial chemoreceptors* in the carotid and aortic bodies are stimulated by hypoxia, hypercapnia or acidosis and cause a decrease in heart rate and an increase in TPR and MAP. The increase in TPR and MAP will be counteracted to some extent by the local systemic vasodilatation. This chemoreceptor effect contributes to the diving reflex and can only be demonstrated in a dive or breath-hold where there is no concurrent increase in ventilation. Stimulation of the peripheral chemoreceptors normally results in an increase in ventilation which will stimulate opposing reflexes from the lung stretch receptors. The final response to breathing an hypoxic gas mixture is an increase in heart rate and in severe hypoxia and a decrease in myocardial contractility, TPR and MAP.

4. *Central chemoreceptors* near the ventral surface of the medulla oblongata are stimulated by hypercapnia and reflexly increase heart rate, TPR and MAP. Most of the increase in TPR and MAP is opposed by local systemic vasodilatation and by the accompanying increase in ventilation stimulating lung stretch receptors.

5. *Limb proprioceptors* believed to be stimulated during exercise send their afferent information to the hypothalamus and cause increases in Q, TPR, MAP and ventilation.

6. *Peripheral and central temperature receptors* also have inputs to the hypothalamus and during an elevated body temperature will reflexly cause an increase in Q, and possibly in MAP, and a decrease in TPR with preferential vasodilatation of skin arterioles.

7. *Laryngeal and tracheal receptors* causing the cough reflex and *epipharyngeal receptors* causing the sniff reflex also cause an increase of short duration in TPR and MAP. In contrast the *lung irritant receptors* of the lower airways have no known cardiovascular reflex.

8. *Juxtacapillary (J) receptors* in the lungs stimulated by local oedema not only cause rapid, shallow breathing but also cause a decrease in heart rate, TPR and MAP.

Cardiovascular Centres

Cardiovascular centres are areas in the brain responsible for the intergration of sensory information and the subsequent control of the autonomic nervous output to the cardiovascular system. They are found in the *pons* and *medulla oblongata* of the brain stem and in the *hypothalamus.* Modification of the autonomic nervous output also occurs as a result of activity in the *cerebral cortex* and *limbic system* descending to the hypothalamus, in *cerebellar pathways* descending to the pons and medulla and in the *spinal cord.*

Until recently the centres in the pons and medulla were considered the principal integrating centres and the description below is a simple version this classical model. However it must be stressed that current research indicates that these centres are not clearly defined and are an important but by no means the only part of a very complicated integrating system extending from the cerebral cortex to the spinal cord.

In the classical model, the principal cardiovascular centres are located in the reticular formation of the pons and medulla rostrally and laterally as the *pressor area* and caudally and medially as the *depressor area.* There is a certain degree of overlap between them. Electrical stimulation of the pressor area induces increases in heart rate, myocardial contractility, TPR, MAP, venomotor tone and adrenaline secretion. The converse effects result from stimulation of the depressor area.

Neurones in the pressor area send axons down the spinal cord to excite preganglionic sympathetic fibres. Those neurones in the pressor area controlling vasomotor tone have some tonic nervous activity and have been referred to collectively as the *vasoconstrictor area.* Those neurones controlling the heart rate have little tone activity and have been referred to as the *cardioexcitatory area.* These areas are functional rather than anatomical since their neurones intermingle throughout the pressor area.

Neurones in the depressor area which have little tonic activity send axons to inhibit preganglionic sympathetic fibres and constitute the functional *vasodilator area.* Neurones in the depressor area which have considerable tonic activity send axons to excite the dorsal motor nucleus of the vagus in the medulla and constitute the functional *cardioinhibitory area.*

The *sensory pathways* of the baroreceptors, atrial 'B' receptors and lung J receptors converge on the depressor area and those of the central chemoreceptors converge on the pressor area. The lung stretch receptors send impulses both to the cardioexcitatory neurones in the pressor area and to the vasodilator neurones in the depressor area, whilst the inputs from nasal, laryngeal and tracheal receptors and peripheral chemoreceptors converge on the cardioinhibitory neurones in the depressor area and on the vasoconstrictor neurones in the pressor area.

Local hypoxia, hypercapnia and acidity in the brain during *ischaemia* are believed to stimulate both the pressor area (particularly its vasoconstrictor area) and the preganglionic sympathetic fibres in the spinal cord.

The *respiratory centres* are also located in the medulla. When the dorsal respiratory group increases its nervous activity to cause inspiration, it also sends impulses to the pontomedullary pressor area (particularly to the cardioexcitatory area) resulting in increases in heart rate during inspiration (*sinus arrhythmia*).

The *cerebellum* not only coordinates movement and orientation but also assists in the postural control of MAP. Stimulation of the cerebellum excites the pontomedullary pressor area resulting in increases in heart rate, TPR and MAP.

Caudal *pressor* and rostral *depressor areas* can be identified in the *hypothalamus* and these project to the corresponding areas in the pons and medulla. Atrial 'B' receptors relay to the hypothalamic pressor area as well as to the supraoptic nuclei of the hypothalamus which control the release of antidiuretic hormone.

The *defence reaction centre* of the hypothalamus, stimulated electricalliy or via the motor cortex in alarm and defence responses, activates the hypothalamic pressor area. This results in increases in Q and MAP together with vasoconstriction of all organs except brain, heart and skeletal musculature. The defence reaction centre also activates, at synapses in the hypothalamus, axons which descend from the motor cortex to the preganglionic fibres of the cholinergic vasodilating sympathetic pathway in the spinal cord.

The *temperature regulating centre* of the hypothalamus in response to an increase in body temperature activates the hypothalamic pressor area causing an increase in Q and a sympathetically-mediated vasoconstriction of all organs except the heart, brain and skin. At the same time the temperature regulating centre decreases the activity in hypothalamic axons controlling the sympathetic adrenergic vasoconstrictor fibres to the arterioles, venules and arteriovenous anastomoses of the skin. The resulting vasodilatation and consequent large blood flow through the skin aids in the restoration of normal body temperature. The balance between the degree of vasodilation in the skin and vasoconstriction elsewhere coupled with the degree of increase in Q will determine the degree of decrease in TPR and MAP. The converse sequence of events occur during a decrease in body temperature.

The *limbic system* integrates many emotional and behavioural reflexes and, via the hypothalamic pressor and depressor area, will elicit the pressor response of excitement or mild pain and the depressor response of shock or severe pain. The *motor cortex* relays to the hypothalamic pressor area during the anticipatory and steady-state phases of exercise as well as activating the cholinergic sympathetic pathway.

11.5 Characteristics of the Circulation Through Different Organs

Pulmonary Circulation

The pulmonary vessels have thinner, more compliant walls and are shorter in length and larger in diameter than the vessels in the systemic circuit. The entire cardiac output flows through the pulmonary circuit whose resistance is about a tenth that of the systemic. In the pulmonary artery the systolic, diastolic and mean pressures are about 25, 8 and 15 mmHg respectively and the pressure declines gradually to about 10 mmHg in the capillaries and to a mean of about 5 mmHg in the left atrium. Thus, in contrast to the systemic circuit, the arterial and venous parts of the pulmonary circuit contribute equally to the total pulmonary resistance. Since the pulmonary resistance is so low, flow remains pulsatile although the pulses decrease in amplitude as blood flows through the pulmonary vessels (Fig. 11.36).

The vast network of pulmonary capillaries in the walls of the alveolis is utilized for gas exchange between the alveolar air and pulmonary blood. The total cross-sectional area of the pulmonary capillaries and hence the velocity of capillary flow are similar to those of the systemic circuit (Fig. 11.36). However, since the pulmonary capillaries are shorter, the transit time through each capillary at rest is about 1 rather than 2 sec. During severe exercise the five-fold increase in pulmonary blood flow is associated with an increase in mean pulmonary arterial pressure which opens up now-perfused lung capillaries and thus increases their cross-sectional area of the pulmonary capillaries but by only 1.5-fold. Hence velocity through the pulmonary capillary increases considerably and the transit time is as little as 0.3 sec. Although this will impede equilibration of gases by diffusion it is not the limiting factor in the supply of O_2 during exercise, at least at sea level.

In the erect posture about 450 mL (about 10% of the total blood volume) is in the pulmonary circuit. Since both pulmonary arterioles and veins are very compliant, the pulmonary circuit accommodates about 16% of total blood volume in the supine position. Pulmonary blood volume also increases passively in exercise, generalized systemic vasoconstriction, left heart failure or mitral stenosis and decrease passively in generalized systemic vasodilatation and haemorrhage. Thus the pulmonary circuit functions as a blood volume reservoir (the *pulmonary reservoir*).

The compliant pulmonary vessels are also subject to a varying transmural pressure induced by the fluctuating intrapleural pressure of respiration. Thus their volume increases during inspiration and decreases during expiration. Powerful expiration or positive pressure breathing can markedly reduce pulmonary (and cardiac) blood volume and pulmonary flow, as well as impeding systemic venous return.

The effect of gravity in the erect posture and the low pressure and high distensibility of the pulmonary circuit results in less, or even intermittent, flow to the apex relative to the base of the lung. The consequence of this for gas exchange and the total ventilation / perfusion ratio of the lung will be considered later.

Although pulmonary arterioles and veins are well supplied with sympathetic vasoconstrictor and parasympathetic vasodilator fibres, their roles are not clear. However, stimulation of the sympathetic system or administration of adrenaline can decrease the pulmonary blood volume by as much as 30%.

Neither myogenic nor metabolic autoregulation is demonstrable in the pulmonary circuit. In fact the response of the pulmonary arterioles to local hypoxia, hypercapnia and acidity is the exact opposite of that of systemic arterioles. *Hypoxia* is the more potent of the three stimuli. In poorly ventilated regions of the lung, where alveolar O_2 is low and CO_2 is high, local pulmonary *vasoconstriction* diverts blood flow to better ventilarted areas. This improves gas exchange by helping to equalize the regional ventilation/perfusion ratios in the lung. However this hypoxic vasoconstriction has the disadvantage that during the hypoxia of altitude or of chronic obstructive lung disease all pulmonary arterioles are affected. The resultant increase in pulmonary resistance increases right ventricular and pulmonary arterial pressure.

Since it is essential for gas exchange that the alveoli do not accumulate liquid, the pulmonary circuit is accompanied by a lymphatic system more extensive than in any other organ. Furthermore the colloid osmotic pressure of 25 mmHg is greater than the difference in hydrostatic pressure between capillary (10 mmHg) and interstitium (-3 mmHg) and favours reabsorption of fluid across the capillary. However accumulation of fluid in the alveoli (pulmonary oedema) may occur and lead to dyspnoea when the left atrial pressure is increased during ldeft ventricular failure or mitral stenosis or when the pulmonary arterial pressure increases during severe exercise.

The airways of the lung from trachea to bronchioles are totally supplied by the systemic aorta via the bronchial arteries. This *bronchial circulation* constitutes only about 1% of the total cardiac output. Some venous drainage (about 25%) is via bronchial veins into the superior vena cava but the remaining 75% enters the pulmonary veins. There are also direct connections between the bronchial and pulmonary capillaries. This intermingling of the two circulations results in a very small degree of O_2 desaturation of the oxygenated pulmonary venous blood. Pathologically, if the pulmonary arterial supply is inadequate, the bronchial arteries can provide some collateral circulation but with consequently more obvious O_2 desaturation.

Coronary Circulation

Since the heart at rest receives about 5% of the cardiac output nad has a very high O_2 consumption relative to its mass, its venous O_2 content is low and there is thus a very large arteriovenous O_2 difference. In contrast to other active organs, during increased cardiac activity there is little further decrease in its venous O_2 content and the increased demand for O_2 is satisfied mainly by a large increase (up to four-fold) in coronary blood flow, a prime example of *metabolic autoregulation.* Hypoxia is a more potent coronary vasodilator than an increase in P_{CO2} or blood acidity.

Although the smooth muscle of the coronary arterioles receives both sympathetic and parasympathetic innervation and contains alpha adrenergic receptors, mediating vasoconstriction, and cholinergic receptors, mediating vasodilatation, the importance of these pathways is not clear. Any neurally induced vasoconstriction occurring during increased sympathetic stimulation is overriden by the metabolic vasodilatation resulting from the simultaneous increase in cardiac activity. Similarly during increased parasympathetic stimulation any neurally induced vasodilatation will tend to be overriden by the metabolic vasoconstriction. Note that adrenaline acting on beta2 adrenergic receptors causes coronary vasodilatation.

The vascular bed of the heart has a very high resistance which is partly due to the *compression* of the blood vessels during cardiac contraction. In systole the peak pressure is about 120 mmHg in the aorta, coronary arteries and left ventricle and about 25 mmHg in the right ventricle. Within the myocardial wall these pressures will be slightly greater. Thus in systole the coronary vessels of the left ventricle are compressed and there is little flow in the left coronary artery, whereas in the right ventricle the transmural pressure of the coronary arteries is only reduced from 120 to 95 mmHg and the right coronary flow is hardly affected. In diastole the pressure in the coronary arteries is about 80 mmHg whilst that in both ventricles is about 0 mmHg. Hence there is no compression of blood vessels in diastole. Left coronary arterial flow is therefore intermittent, ceasing in systole, and right coronary arterial flow is pulsatile, being slightly greater in systole than in diastole. Venous flow through the coronary sinus into the right atrium is greatest during the compression of systole and subsides during diastole.

Taking into account that diastole occupies about two-thirds of the cardiac cycle at rest, about 80% of the total, about 85% of the left and about 70% of the right coronary arterial flow occurs during diastole. Furthermore left coronary arterial flow is about 60% of the total flow. With tachycardia, which reduces the period of diastole considerably, and with an increased myocardial contractility, a greater proportion of the coronary resistance arises from compression and coronary arterial flow is impeded for shorter but more frequent intervals.

Since about 80% of the total coronary blood flow occurs during diastole, the aortic diastolic rather than the mean arterial pressure becomes the primary determinant of the pressure gradient for coronary flow. Furthermore, coronary arterioles exhibit *myogenic autoregulation* such that coronary flos at rest is constant in the aortic diastolic pressure range of 60 to 180 mmHg. However, if the aortic diastolic pressure increases as a result of an increase in cardiac activity, coronary blood flow will increase through metabolic autoregulation.

Reductions in coronary blood flow can be caused by a low aortic diastolic pressure as in cardiac failure or haemorrhage, by a rise in atrial and ventricular diastolic pressures as in cardiac failure, by a high left ventricular systolic pressure as in aortic valve stenosis or by atherosclerosis of the coronary vessels. The resultant *myocardial ischaemia* affects mainly the left ventricle.

Cerebral Circulation

The soft tissue of the brain, covered by a highly vascular arachnoid membrane and a tough dura mater, is encased in the rigid skull. *Cerebrospinal fluid (CSF)* fills both the four ventricles and the subarachnoid space between the arachnoid and the pial surface of the brain. The CSF is in continuity with the interstitial fluid of the brain and is formed from the plasma by the capillaries of the brain, particularly those in the choroid plexuses. CSF flows in a specific direction around the brain and is reabsrobed from the subarachnoid space through the arachnoid villi into the venous sinuses of the dura. There is no lymphatic system in the brain. Its drainage function is taken over by the CSF.

From the vertebral and internal carotid arteries are derived the arteries of the brain which, until they branch and penetrate the brain, lie close to the pia amongst the trabeculae in the subarachnoid space. Venules drain into the superficial veins of the pia which in turn drain either into the venous sinuses in the dura before entering the internal jugular veins or into the vertebral veins of the spinal cord and thence to the external jugular veins. Unlike other capillaries, those of the brain (except in the circumventricular organs) are relatively impermeable to most substances except fat-soluble drugs, glucose, O_2 and CO_2. This impermeability is referred to as the *blood-brain barrier*.

The brain receives about 15% of the cardiac output, has a moderately resistant vascular bed, a fairly high O_2 consumption and a large arteriovenous O_2 difference. *Total blood flow* through the brain remains remarkably *constant* under physiolgic conditions. However, the normal variations in nervous activity within regions of the brain are associated with alterations in regional blood flow brought about by local metabolic autoregulation.

The control of cerebral blood flow (CBF) is highly developed. Although the cerebral arterioles are innervated by the sympathetic and parasympathetic nervous system, there appears to be no significant role for them in vascular control. In contrast *myogenic autoregulation* maintains CBF remarkably constant in the MAP range of about 50 to 150 mmHg. Furthermore *metabolic autoregulation* maintains a constant O_2 supply. Between the normal arterial P_{O2} of 100 mmHg and an hypoxia of 50 mmHg P_{O2} there is little increase in CBF. Below 50 mmHg P_{O2} the cerebral arterioles are sensitive to the vasodilating effects of hypoxia and CBF increases about two-fold as PO_2 decreases from 50 to 25 mmHg. However the cerebral arterioles are much more sensitive to the slightest increase or decrease in arterial P_{CO2} and acidity. Considerable vasodilatation occurs when P_{CO2} is elevated (40-100 mmHg). Within such limits a doubling or halving of P_{CO2} results in about a two-fold change in CBF. The dizziness felt after excessive hyperventilation is the result of the reduced CBF which accompanies the resultant hypocapnia. Since a reduced O_2 supply is usually accompanied by an increase in arterial P_{CO2} and acidity (except at altitude), the CBF is regulated by hypercapnia rather than hypoxia to maintain a constant O_2 supply.

If the O_2 content of arterial blood declines sufficiently or if the MAP drops below the range of myogenic autoregulation such that CBF decreases, the O_2 delivery

to the brain is impaired. This precipitates a sudden state of *unconsciousness* which if it is of short duration is a *faint* but if prolonged is a *coma* and is often accompanied by brain damage. An obstruction or a rupture in a major cerebral artery (a *stroke*) leads to local areas of brain *ischaemia* (reduced blood supply) and often to local areas of brain damage.

Intracranial pressure also affects CBF. Since fluid is essentially incompressible, the volume of blood, brain tissue and CSF within the rigid cranium must be essentially constant (the *Monro-Kellie doctrine*). An increase in intracranial pressuree (i.e. the pressure of the CSF) caused by insufficient reabsorption of CSF or a blockage in its normal route of flow, will thus compress cerebral vessels and reduce CBF. The consequent hypoxia and hypercapnia will stimulate directly the pressor area of the cardiovascular centre and the resultant rise in MAP, coupled with local cerebral vasodilatation, will tend to restore CBF. At the same time, the rise in MAP will reflexly decrease heart rate via the baroreceptors. These reflex responses to an increased intracranial pressure are called the *Cushing reflex*. There is obviously a limit to the increase possible in MAP and if intracranial pressure exceeds this in the clinical state of severe *hydrocephalus* the cerebral circulation ceases.

A further consequence of the Monro-Kellie doctrine is that increases in cerebral blood pressure caused by *gravity* during a head-stand, together with any tendency to an increase in cerebral venous volume, are transmitted to the CSF such that intracranial pressure also increases. Thus little change occurs in the transmural pressure and cerebral venous return decreases only slightly. Conversely in the erect posture the decreases in cerebral blood pressures are compensated for by a corresponding fall in intracranial pressure. Furthermore the major cerebral veins can not collapse because they are held open by their association with the dura mater.

Cutaneous Circulation

At rest the skin receives about 8% of the cardiac output through its relatively highloy resistant vascular bed. Since it has a very low O_2 consumption, the arteriovenous O_2 difference is also small. The skin has na extensive superficial network of arterioles, capillaries and venules and an extensive *deep plexus of veins*. The latter may contain up to 1.5 L of blood. The arterioles and veins are richly innervated with sympathetic fibres acting via *alpha adrenergic* receptors and hence the vascular resistance and capacitance of the skin can be altered by reflexes integrated by the cardiovascular centres in the pons and medulla. For instance during hypotension, haemorrhage, or exercise that does not generate a heat load, the blood flow to the skin can be restricted, making it feel cold, and the accompanying venoconstriction mobilizes a sizeable volume of blood from the deep venous plexus of the skin.

In the skin of the hands, feet and face (particularly the ears, nose and lips) there are also large numbers of *arteriovenous anastomoses*. These are vessels about 50 micom in diameter with thick walls of smooth muscle which contain *alpha adrenergic* receptors activated by sympathetic fibres. When *body temperature* is increased sympathetic activity to the skin decreases under the control of the hypothalamus, resulting in vasodilatation particularly of these arteriovenous anastomoses. This

vasodilatation is enhanced by the *bradykinin* released by sweat glands when these are activated by cholinergic sympathetic fibres also originating from the hypothalamus. The large fall in total peripheral resistance, reflexly via the baroreceptors, triggers a corresponding increase in cardiac output. The massive increase in skin blood flow is accompanied mainly within the arteriovenous anastomoses and the venous plexuses which together provide a large area for heat exchange between the blood and the skin, and hence the external environment. Thus the temperature of the body is regulated to a large extent by the amount of blood flowing through the skin which, from the thermoneutral point, can increase about thirty-fold in heat stress and decrease about ten-fold in cold stress.

Skin tissue, to a much greater extent than other tissues, can tolerate reduced blood flow by *reducing its O_2 consumption* accordingly. However too great a reduction during prolonged exposure to cold leads to skin death (*frost-bite*). During less severe but prolonged exposure to the cold, the skin vasoconstriction changes to vasodilatation which explains the ruddy complexion on a cold day. This vasodilatation is not sympathetically mediated but is believed to be caused by *metabolic autoregulation*, which now overrides sympathetic control, and by damaging skin cells elicits an exon-axonal reflex. Note that skin arterioles are incapable of myogenic autoregulation.

The alpha adrenegic sympathetic pathway to skin vessels is also activated via the hypothalamus by various *emotions* made manifest in blushing or in the pallor axxompanying fear.

In the skin the reactions of blood vessels can easily be observed. A pointed object drawn lightly over the skin causes the area of contact rapidly to become pale (the white reaction). The mechanical stimulation is thought to initiate local contraction of venules or precapillary sphincters. Greater pressure will cause the skin rapidly to become red (the red reaction), followed by a diffuse mottled reddening around the area of injury (the flare) and then a local swelling (the weal). The latter three reactions comprise the so-called *triple response.* The red reaction probably results from the damaged cells of the skin releasing substances like histamine which cause a local vasodilatation or venodilatation. The flare results from the mechanical stimulation of sensory endings causing antidromic conduction in axon branches (axon-axonal reflex) that release substance P (a vasodilator) near arterioles. The weal results from a histamine-induced increase in permeability of the capillaries.

Skeletal Muscle Circulation

Skeletal musculature receives at rest about 15% of the cardiac output through a highly resistant vascular bed, the tone of which is controlled by *myogenic autoregulation* and by sympathetic activity predominantly acting on *alpha adrenergic receptors.* Becuase of its large mass (about 50% of body weight but about 90% of the total cellular mass) it consumes even at rest about 20% of the total O_2 consumption.

During maximal exercise, skeletal musculature receives about 90% of the cardiac output and also consumes about 90% of the O_2 consumption. The concomitant

vasodilatation in the skeletal musculature results from *metabolic autoregulation*. The vasodilatation from adrenaline acting on *beta2 adrenergic receptors* and from the *cholinergic sympathetic pathway*, which originiates in the hypothalamus, plays little role once exercise is established. In rhythmic exercise blood flow in the muscles concerned can cease during the contraction phase but because of the accumulation of metabolites it is then augmented during the relaxation phase. In non-rhythmic, especially isometric exercise, blood flow can cease entirely thus limiting the duration of such exercise.

Non-exercising skeletal musculature, because of its large mass, is an important site for sympathetic vasoconstriction mediated via alpha adrenergic receptors during reflexes initiated for example, by hypotension or haemorrhage. In contrast to splanchnic and cutaneous veins, the veins in skeletal musculature are practically devoid of sympathetic nerve endings and cannot alter their capacity neurogenically so as to contribute to the blood reservoir.

Splanchnic Circulation

The splanchnic area receives through a low resistance vascular bed about 25% of the cardiac output at rest. A number of arterial branches from the abdominal aorta supply the stomach, intestine, pancreas and spleen which are drained by the portal vein into the liver. The liver receives about 75% of its blood from this source, the remainder coming from the hepatic artery. Blood from the liver drains via hepatic veins into the inferior vena cava.

In the splanchnic and hepatic arteries the mean blood pressure is about 90 mmHg whilst in the portal and hepatic veins it is 10 and 5 mmHg respectively. The hepatic arterioles are higly constricted and consequently blood enters the relatively large liver capillaries or sinusoids at a pressure less than 10 mmHg. This vasoconstriction and hence the proportion of *blood flow to the liver* from the hepatic artery is controlled by myogenic and metabolic autoregulation. There is also vasomotor tone from sympathetic fibres acting via alpha adrenergic receptors. Increased metabolic activity in the liver or a decrease in portal flow will, via *metabolic autoregulation,* increase flow in the hepatic artery such that it can supply up to 50% of the blood flow to the liver. Conversely an increase in portal flow will decrease flow in the hepatic artery via *myogenic autoregulation*. Note that the low hydrostatic pressure in the capillaries of the liver is matched by the high interstitial colloid osmotic pressure generated by the proteins which are being manufactured by the liver for the plasma. Hence the Starling forces for ultrafiltration and reabsorption across the capillary wall remain in balance.

Blood flow to the gut is adjusted to the degree of activity in the smooth muscle layers by *metabolic autoregulation* and in the mucosa and submucosal layers by increased glandular activity releasing *bradykinin* which causes local vasodilatation.

The *alpha adrenergic receptors* in the splanchnic arterioles and veins mediate vasoconstriction and venoconstriction in response to the generalized increased sympathetic activity and adrenaline secretion that occurs, for instance, during

exercise, hypotension or haemorrhage. This serves to counteract a fall in mean arterial blood pressure and to redistribute blood to other vasodilated regions. Furthermore the reduction in *splanchnic venous capacity* can make about 300 mL of blood available to the rest of the body. Venous reservoirs of blood are also found in the spleen of some animals, for example the dog, but not in man. However, since prolonged splanchnic vasoconstriction would lead to cell damage in the gut, accumulation of metabolites will eventually override some of the vasoconstriction.

Renal Circulation

The kidney receives through a very low resistance vascular bed about 25% of the cardiac output. The arterioles of the isolated kidney exhibit well-developed *myogenic autoregulation* such that kidney perfusion is maintained constant at mean arterial blood pressures between 80 and 180 mmHg. Thus the renal functions of filtering waste products and regulating electrolyte balance are independent of fluctuations in blood pressure. However *in situ* this myogenic autoregulation can be overriden by sympathetic activity and adrenaline acting on *alpha adrenergic receptors* of the kidney arterioles. Normally there is little sympathetic tone but during exercise, hypotension, haemorrhage or systemic hypoxia and hypercapnia, the renal arterioles participate in the vasoconstriction that ensures adequate cerebral and coronary circulation. Furthermore during exercise or heat stress, renal vasoconstriction helps to compensate for the vasodilatation in skeletal musculature or in the skin. Metabolic autoregulation in the renal circulation is poor.

11.6 Cardiovascular Adjustments Under Physiological and Abnormal Conditions

The cardiovascular system has to adjust to the strains imposed by alteration in posture, by thermal stress and by exercise. The cardiovascular system also has to compensate for the abnormalities induced by hypertension, hypotension, haemorrhage and cardiac failure.

Effects of Posture

The pressures and volumes in the heart of Fig. 11.19 apply to the standing posture whilst the pressures and volumes in the vascylar system of Fig. 11.36 apply to the supine posture. A change in posture alters the hydrostatic pressures in the blood vessels with resultant effects on transmural pressures and, in particular, on venous capacity and consequently on the distribution of blood around the cardiovascular system. Thus in turn affects end-diastolic volume.

Hydrostatic Pressure

In the supine posture all bloods vessels are approximately at the level of the heart and the mean blood pressures in the aorta, the arteries and veins of both the head and feet and in the right atrium are about 100, 95, 5 and 1 mmHg respectively. In the standing posture the weight of the column of blood in the blood vessels results in an increase in arterial and venous pressure below the level of the heart and a decrease in these pressures above the level of the heart. For every cm of blood above

or below the level of the heart, pressure changes by 0.77 mmHg. Thus in a man 1.8 m tall in whom the head is about 50 cm above the heart in the upright posture, there is a fall in blood pressure in the head of about 40 mmHg compared with the pressure in the supine position. Hence the arterial pressure at the entrance to the cranial cavity becomes 55 mmHg and, were it not for the fact that the veins in the neck collapse, the venous pressure at the cranial exit would be -35 mmHg. In the feet, which are about 130 cm below the heart in the standing posture, there is an increase in pressure of about 100 mmHg and hence the arterial pressure becomes 195 mmHg and the venous pressure becomes 105 mmHg, provided that in the case of the veins the standing is motionless.

It must be noted that blood flows from a point of high to low total fluid energy. The total fluid energy is the energy generated by the heart plus the gravitational hydrostatic energy plus the gravitational potential energy. The latter two energies are equal but opposite. Thus the total fluid energy in the arteries of the feet is the equivalent of 95 mmHg irrespective of a supine or standing posture. Therefore the changes in blood pressure on adoption of the standing posture do not mean that blood flow against a hydrostatic pressure, for instance from the heart (100 mmHg) to the arteries in the feet (195 mmHg). Nor does it mean that it is difficult for blood to return from the feet to the heart.

Transmural Pressure and Venous Capacity

If blood vessels were rigid tubes, no cardiovascular adjustments to the standing posture would be required other than to compensate for decreased blood volume due to enhanced filtration across the capillary wall. However the changes in the blood pressure and hence in transmural pressure affect, in particular, the veins which tend to empty and so collapse above and progressively fill below the level of the heart.

The collapse of veins in the neck breaks the column of blood and hence removes the effects of gravity and the venous pressure approximates to zero. The veins although collapsed are not always occluded as flow can continue unimpaired through spaces formed where the walls are not in total apposition. Blood which does accumulate behind the areas of collapse raises the pressure sufficiently above zero to cause intermittent venous flow. Intracranial veins do not collapse because the CSF and blood are affected equally by gravity and because the venous sinuses are maintained patent by the dura. Thus the cerebral blood flow is dependent only on carotid artery pressure, the venous pressures at the exit being zero at all times.

Irrespective of posture, if the mean right atrial pressure equals about 1 mmHg, the height of the uncollapsed column of blood in the jugular vein is always abvout 1.5 cm *vertically* above the rigth atrium (which is approximately at the level of the sternal angle). A greater *length* of uncollapsed vein can obviously be seen the more tilter the subject is towards the supine position. The vertical height of this blood column is used clinically as a measure of central venous pressure and the pulsations of the a, c and v waves can sometimes be distinguished at the top of the column.

Initially on assuming the standing posture the passive distension of veins below the level of the heart results in an increase of about 500 mL in the volume of blood that they contain, most of this being displaced from the thorax. Consequently, in the absence of reflex compensations, there is a reduction in venous return and end-diastolic volume and hence in stroke volume and systolic blood pressure. Furthermore the increased hydrostatic pressure in the capillaries below the level of the heart will cause considerably more ultrafiltration than usual and over a period of hours this will lead to loss of blood volume and, most noticeably, to local oedema in the ankles.

Reflex Compensations

The decrease in end-diastolic volume is detected by the cardiac stretch receptors and the decrease in MAP (from both the direct gravitational effect at the level of the carotids and the decrease in cardiac output) is detected by the carotid baroreceptors. In the space of about 5 sec there are thus reflex increases in sympathetic activity and in adrenaline release causing (i) an increase in heart rate and in myocardial contractility tending to restore cardiac output towards the supine value; (ii) vasoconstriction in the skeletal musculature, skin, kidneys and gut reducing blood flow to these organs, increasing TPR and decreasing capillary pressure, and (iii) venoconstriction in all veins but in particular in the skin and gut which displaces some blood back to the thorax. All of these contribute to the restoration of MAP at the carotid level.

Over a longer period of time, the cardiac stretch receptors will trigger an increase in antidiuretic hormone secretion. The reduced blood flow to the kidneys enhances the release of renin which increases circulating concentrations of angiotensin II and aldosterone. These responses, which are similar to those occurring after a mild haemorrhage, augment vasoconstriction and decrease urinary Na^+ excretion which helps restore blood volume.

One of the most important mechanisms counteracting the long-term effects of the standing posture is the use of the skeletal muscle venous pump. This, aided by the venous valves, reduces venous capacity and assists venous and lymphatic returns thus lowering the mean venous pressure in the feet from about 1095 mmHg to as little as 30 mmHg. The normal muscular contractions associated with moving around in the standing posture are sufficient to achieve this and hence there is less of an increase in venous capacity and little local oedema. Prolonged standing, venous obstruction or pregnancy can overstretch the veins and lead to incompetent venous valves. The consequent ineffectiveness of the skeletal muscle venous pump results in the excessive distension of, in particular, superficial veins which fill with static blood - the condition known as *varicose veins.*

During motionless standing or in sudden standing of hypotensive patients or of patients with an impaired sympathetic systm or of subjects in a hot environment where venodilatation in the skin predominates, restoration of the MAP may be inadequate. If the MAP declines to a level (about 50 mmHg) below which myogenic autoregulation of cerebral blood flow cannot occur, the person becomes dizzy, has

impaired vision and may even faint. *Fainting* has the advantage of returning the person to the supine position!

Hypertension

Repeated measurements of arterial diastolic pressure above 90 mmHg in the resting supine object are taken clinically to indicate the condition of *hypertension*. It is associated with increases in Q or TPR or both. Clinically hypertension is classified as primary or essential (95% of cases) and secondary or symptomatic. The causes of *primary hypertension* are not clear but may include (i) hereditary factors, (ii) a large Na+ intake in the diet and (iii) psychological factors. *Secondary hypertension* can be the result of (i) a renal disease causing renal vasoconstriction, reduced renal blood flow, the release of renin and a consequent increase in blood volume, (ii) endocrine disorders leading to increased adrenaline secretion resulting in Na+ retention or (iii) toxaemia in pregnancy. In hypertensives the baroreceptor reflex modulates MAP around an elevated set-point. Hypertension can lead to further renal damage, more severe hypertension, congestive heart failure and strokes.

Hypotension, Fainting and Shock

Arterial systolic pressures below 100 mmHg can be taken to indicate *hypotension*. Such pressures are associated with decreases in Q but sometimes with decreases in TPR and occasionally in both. Hypotension may be the result of (i) endocrine disorders, for example Addison's disease, (ii) cardiovascular disorders such as aortic or mitral stenosis or cardiac failure, (iii) loss of tone in resistance and capacitance vessels, (iv) allergic or toxic reactions causing vasodilatation and (v) haemorrhage.

The commonest manifestation of acute hypotension is *fainting* (syncope), which is the sudden loss of consciousness due to cerebral ischaemia. It is usually of short duration since the resulting supine position helps elevate the MAP. Fainting can also result from a sudden bradycardia and diffuse vasodilatation often precipitated by a strong emotion (referred to as a vasovagal syncope) or by sudden pressure exerted on the neck in the region of the carotid baroreceptors. Furthermore fainting can ensue (i) in certain instances after adoption of the standing posture; (ii) if the intrathoracic pressure is raised sufficiently enough, by coughing or by straining in defaecation, to impair venous return; and (iii) if the increase in Q during exercise is not sufficient to compensate for the vasodilatation in the skeletal musculature.

Hypotension only becomes critical when inadequate blood flow disrupts organ function. This is referred to as *shock*. The signs of shock are pallor, coldness and sweating of skin, collapse of superficial veins, hyperventilation, tachycardia, reduced urine formation, thirst, decreased body temperature, decreased metabolism and metabolic acidosis. If shock is untreated or sufficiently severe, it is likely to become irreversible with severe hypotension, unconsciousness, CNS damage, hypoventilation and further reductions in Q which will lead eventually to respiratory and cardiac failure and to death. Inadequate cardiac output can arise either from sudden failure

of the heart to pump as in coronary occlusion or from a severe reduction in blood volume due to dehydration, haemorrhage or plasma loss resulting from burns.

Haemorrhage

Loss of 10% of the blood volume (about that given by a blood donor) is easily compensated for and thus results in little change in MAP. Loss of up to 30% over a relatively brief period (i.e. 30 min) will cause a fall in MAP to about 70 mmHg and signs of mild shock. The cardiovascular reflexes initiated by such a fall eventually will compensate completely for the loss of blood volume. However the rapid loss of a greater volume of blood will result in severe shock which may become irreversible if not treated by blood transfusion or by raising the blood volume by administration of a fluid with similar colloid osmotic pressure to plasma.

Following a *haemorrhage* the decrease in blood volume reduces end-diastolic volume and hence stroke volume, Q and MAP. Detection of these reductions by the cardiac stretch receptors and arterial baroreceptors will result in an immediate increase in the secretion of angiotensin II, antidiuretic hormone and aldosterone. The consequent responses are the same as those which follow a change from the supine to the erect posture but are of greater magnitude. These responses may serve to restore Q and MAP towards normal. Further restoration can only occur by restoring the blood volume. After about 15 min at least 500 mL of plasma volume will have been provided by the transfer of interstitial fluid into the capillaries as a consequence of the reduced capillary pressure that has resulted from the hypotension itself and the vasoconstriction. In the next few hours further restoration of circulating volume occurs because of the increased Na^+ retention by the kidneys and the resultant quenching of thirst. In contrast replacement of the plasma proteins by synthesis requires 3 to 6 days and the formation of new erythrocytes takes 4 to 6 weeks.

The progress of these adjustments to haemorrhage can be examined using the graph of ventricular and systemic vascular function curves. In Fig. 11.49 position A is the normal pre-haemorrhagic value, Q being about 6 L / min and mean right atrial pressure about 1 mmHg. Immediately after the loss of about 25% of the blood volume the new position will be indicated by point B which lies on the normal ventricular function curve but on a systemic vascular function curve which is shifted substantially downwards. The reflex increase in myocardial contractility moves the ventricular function curve upwards and steepens it and at the same time the reflex venoconstriction moves the systemic vascular function curve upwards. Thus position C is reached. After about 15 min, restoration of some of the lost volume will move the systemic vascular function curve upwards still further and the improved MAP will result in less sympathetic drive to myocardial contractility and hence a flatter ventricular function curve. Thus position D will be reached. After a few more hours the cardiovascular system will have returned to the original position of A.

Cardiac Failure

Substantial *cardiac failure* (ventricular failure) most commonly results from impaired coronary perfusion (ischaemic heart disease) usually caused by coronary

atherosclerosis (thickening and hardening of the arterial wall), from disease of the heart valves and from hypertension. However a mild reduction in coronary perfusion may only cause *angina pectoris* which is the term applied to the pain arising from temporary disparity between myocardial O_2 demand and O_2 supply and which may be triggered by exercise in hypertensives.

In heart failure myocardial contractility is insufficient to eject an adequate stroke volume. Thus Q and MAP are decreased, blood accumulates in the venous sides of the circulation with consequent elevation of venous pressures. The heart is engorged with unejected blood and end-diastolic volume and right and left atrial pressures increase. Furthermore inadequate organ perfusion and even shock may result. The decreased Q reduces renal blood flow so that Na+ and water are retained. When fluid retention reaches 3-4 L, oedema results as a consequence of the disturbances in the Starling equilibrium. Pulmonary congestion and oedema are exaggerated by left ventricular failure in which the large increase in left atrial pressure causes considerable passive expansion of the pulmonary vascular bed. Respiratory symptoms that may accompany cardiac failure are cyanosis and hyperventilation particularly dyspnoea.

The sequence of events in cardiac failure can be examined using the ventricular and systemic vascular function curves. Acute myocardial failure results in position B on a flatter ventricular function curve. The accumulation of blood on the venous side shifts the systemic vascular function curve upwards and so position C is achieved. The next stages involve reflex adjustments. Arterial baroreceptors detect the hypotension and their reflexes dominate the opposing reflexes triggered by the increased end-diastolic volume detected by the cardiac stretch receptors. The increases in sympathetic activity and adrenaline release result in tachycardia, increased myocardial contractility, vaso- and venoconstriction. However, though position D might be reached with upward shifts of both curves, the failing ventricle may be unable to respond to the increased sympathetic drive or to cope with the relative increase in afterload and thus position Z rather than D may eventuate. Steepening the ventricular function curve by the clinical administration of digoxin may help here.

A further problem during cardiac failure lies in the fact that reduced renal perfusion increases renin release and hence circulating angiotensin II and aldosterone. The consequent fluid retention and oedema shifts the systemic vascular function curve upwards still further. This retained fluid volume can be reduced by the clinical administration of diuretics and the capacitance of the vascular system can be increased by the administration of vaso- and venodilatating drugs. If this is successful the systemic vascular function curve will move downwards, the ventricular function curve will move upwards and position E and finally the original position A with a normal mean systemic filling pressure will be achieved.