

## CHAPTER 9.

## THE EXTRAVASCULAR CIRCULATION.

The maintenance of a constant internal environment for the individual cells of the organism, has been accepted as a prime function of the circulation since the original concept put forward by Claude Bernard suggesting the importance of the liquid 'milieu interieur' surrounding the individual cells and diffusing throughout the tissues. This constant internal environment is achieved by continuous exchange of fluid containing salts, nutrients, and dissolved gases between the blood plasma and the fluid in the extra-vascular extracellular compartment. The conditions under which the exchange occurs, and the circumstances controlling it, must then become of central importance to the function of the circulation. The relationship between circulatory function and the exchange which regulates the extracellular environment is the subject of this chapter.

Exchange between the blood and the extra-vascular fluid occurs for the most part from the small vessels of the capillary bed, and the importance of the plasma proteins in this process was emphasised by Starling (1899). Because the capillary wall is readily permeable to water and crystalloids, fluid containing these substances and dissolved gases, pass freely from the capillary to the extra-vascular compartment as a result of the hydrostatic pressure produced by cardiac activity. Provided the partial pressure of oxygen is sufficient to maintain it, the capillary wall is not permeable to plasma protein and other colloids of similar molecular size, and the osmotic pressure exerted by these colloids increasingly resists the hydrostatic pressure in the capillaries until no further fluid is able to leave the blood vessel.

The fluid which has left the vascular system has flow energy which also leaves the intra-vascular compartment, so the hydrostatic pressure falls rapidly as the blood passes through the length of the capillary, and at the venous end, the osmotic pressure exerted by the plasma proteins now exceeds the hydrostatic pressure, and fluid enters the capillary once more, reducing the plasma protein concentration to its original level, and providing the necessary energy to sustain venous flow towards the heart. As this fluid re-enters the blood vessel, it still retains energy of flow, which now gives flow energy to the venous blood.

*Bypassing the capillary network.*

By the nature of its formation by filtration from the blood plasma at the 'arterial end' of the capillary, and its reabsorption after the hydrostatic pressure has fallen while the osmotic pressure exerted by the plasma proteins has been increasing at the 'venous end', a certain amount of fluid must avoid passing through the whole length of the capillary. This is the fluid which constitutes the 'extra-vascular circulation'.

The volume of the extracellular extra-vascular fluid is about three or more times that of the intra-vascular compartment, and is constantly undergoing exchange with both the fluid of the blood and also the intracellular fluid. The rate at which this exchange takes place is of importance in the normal nutrition of the tissues, although gas exchange is normally by diffusion rather than as

dissolved gas in the case of oxygen, while in large part carbon dioxide is held in chemical combination either as part of the 'alkali reserve' or as a carbamino- compound with haemoglobin. In either case carbon dioxide has first to enter the blood for access to haemoglobin or carbonic anhydrase for the above conversions to take place, either at all, or in the latter case, with sufficient rapidity to dispose of any sudden excess production of carbon dioxide.

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The exchange of fluid which occurs between the intra and extra-vascular compartments in the capillary region, is not only essential to the nutrition and metabolism of the tissues, organs, and individual cells, but it is also an integral part of the energy exchange with which the circulatory system is essentially engaged.

The work done by the left ventricle per beat ( $Q \cdot AP$ ) appears partly as potential energy of pressure, and partly as kinetic energy, represented by the flow rate in the vessels. The conversion of potential energy to kinetic energy, is largely accomplished in the aorta and arterial system, and the portion of arterial pressure which is converted to kinetic energy is represented by the pulse pressure. Kinetic energy in the whole systemic circulation is  $\bar{v} \cdot vx \cdot R'$  ( $\propto$  pulse pressure) so that the energy per ml. of systemic blood is  $\bar{v} \cdot Q'$ , the product of 'average mean' linear velocity, and the corresponding 'stroke volume' for each ml. of systemic blood volume (terms which have been explained and defined in previous chapters). This resistance is largely brought about by passage of the blood through the arterioles and capillaries in the first instance, but passage of fluid through the extra-vascular space also contributes to it.

The momentum of a given volume of blood of given density, will depend on its linear velocity, and the momentum of that given volume will remain constant unless the velocity is altered by transfer of energy to some other system, or volume of blood. As each ml. of blood reaches the capillary network its velocity is slowed, and energy is either absorbed by extra force exerted on the walls of the blood vessels as increased lateral pressure (which the vessel wall must resist if it is to remain intact) or energy must be transferred through the vessel wall to the volume of extra-vascular fluid beyond it. The 'average mean' linear velocity of blood in the systemic circulation, is of the order of 10 mm. per second, while the velocity in the capillaries is much lower, of the order of 0.5 mm. per second. This implies that a large part of the momentum of each ml. of blood has been transferred elsewhere. Whether the transfer of energy is to the vessel wall, or to the extra-vascular fluid, depends on the ratio  $R/IPR$  (the vascular index) the significance of which has been discussed already, especially the significance for the integrity of the blood vessels.

The extra strain on the blood vessel walls is reduced if the energy is transferred to the extra-vascular fluid by giving velocity to fluid entering that compartment from the 'arterial end' of each capillary, and then returning to the intra-vascular compartment at the 'venous end'. Momentum is thereby transferred to the extra-vascular fluid in one area, and returned from it in another, creating circulation of the fluid on the one hand, and increasing the momentum of venous blood on the other. The force creating fluid circulation, is the lateral pressure of fluid in the capillaries generated because of falling linear velocity. This force produces protein-free filtrate from the blood plasma, while 'storing' potential energy in the plasma by increase in the osmotic pressure of the more concentrated plasma proteins. The 'solid elements' of the blood, i.e. the blood cells, plus the protein

enriched plasma, are then able to pass through the capillary at reduced velocity, and without extra strain on the capillary walls, but yet allowing adequate momentum to be developed by the venous blood, so that the volume flow rate is maintained, with the venous return matching the ventricular output. This is achieved by allowing flow energy to bypass the capillary system, while aiding in the provision of nutrients (including gases) passing to and from the individual cells. It will be evident that the metabolism of these cells will be dependent in large degree upon the rate of turnover of fluid in the extra-vascular compartment.

If fluid is able to bypass the capillary network, the overall resistance to flow must be reduced, and this helps to explain the findings of Whittaker and Winton (1933) on resistance to flow in the hind limb of the dog. These observers found the resistance to be less *in vivo*, than was predicted by results *in vitro* using a viscometer. In the latter case, the apparent viscosity as measured was twice as great as that measured for the circulation of the hind limb. This suggests that the extra-vascular flow requires less energy than similar flow confined to the blood vessels, even though axial flow allowing blood cells to pass through small vessels at a greater linear velocity than that of the plasma is also a factor in reducing apparent viscosity, (Fahraeus and Lindquist, 1931). While the cells are travelling through the capillaries at a greater linear velocity than the plasma, much of the fluid of the blood plasma, by passing through the extra-vascular space, arrives at the venous end of the capillary for reabsorption at much the same time as the cells from which it was separated at the arterial end, (see also Fahraeus, 1929).

Despite what has been said, the extra-vascular fluid has restraints placed on its general mobility which it is well to recognise here (see Aukland and Nicolayson, 1981). These restraints are imposed by the basic architecture of connective tissue, which is the tissue in which the extra-vascular fluid is contained. The volume of this fluid is comparatively large, usually about 15% (or up to 25%) of the body weight. Free movement of such a volume of fluid within the tissue spaces could produce considerable difficulties for the body as a whole, which the structure of connective tissue limits in degree, but in a general fashion, and not necessarily locally between the capillaries and the cells of the region which they supply. This means that the extra-vascular fluid has limited mobility as to general location, but not with respect to the local dynamics of flow.

The cell content of the connective tissue is low, and the tissue is built upon a skeleton of collagen fibres which may occupy from 3% up to 30% of the nett volume. The space between the cells and collagen fibres consists of water, salts, protein, and glucosamino glycans. It is mainly the latter which restricts the free movement of extra-vascular fluid generally. By maintaining the general distribution of extra-vascular fluid in the face of altered local activity, gravity effects and so on, this structural limitation of fluid movement is essential to the adequate performance of the extra-vascular circulation, which can still function with little restriction at a local level. It is the summation of these local movements which produce the extra-vascular circulation in the overall sense in which it is used throughout this examination.

Restriction of free general movement of extra-vascular fluid is not without its problems. For example, especially active areas of metabolism or physical activity, might lead on occasion to accumulations of fluid (oedema) which are locally restrictive. Equalising distribution of fluid

between such areas, becomes a prime function of the lymphatic system, which in the absence of local damage, can remove such aggregations of fluid, irrespective of their protein or other 'osmotic' content.

Considered as a whole the flow conditions which exist in the extra-vascular compartment, will depend on the volume of fluid in that compartment, and on the total momentum imparted to it (which in turn determines the linear velocity of the fluid bathing the individual cells).

The extra-vascular circulation is a fundamental part of the systemic circulation. It is therefore necessary to consider in detail the circumstances which determine these circulatory conditions. Because the linear velocity of blood in the capillaries is considerably less than the average mean linear velocity for the remainder of the systemic circulation, and as the lateral pressure exerted in the capillaries is falling rapidly between the 'arterial' and 'venous' ends, it would seem that most of the momentum of the circulation is able to pass to the extra-vascular compartment, so that  $D.V_s.v$  is proportional to  $D_x.V_x.v_x$  (where  $V_x$  is the volume of the extra-vascular extracellular compartment, and  $v_x$  is the corresponding average mean linear velocity of the fluid in that compartment, which has density  $D_x$ ). The work done by the heart per beat after overcoming peripheral resistance, is  $V_s.v.R$  and becomes proportional to  $V_x.v_x.R$ . This work will be equivalent to the work done in the extra-vascular compartment which can be represented as  $V_x.OPP$ . (where  $OPP$  is the reabsorptive pressure to which the extra-vascular fluid is subjected, and can be designated as the effective osmotic pressure of the plasma proteins, or nett algebraic sum of the hydrostatic pressures inside and outside the vessels together with the osmotic pressures in the same areas). From this is obtained a relationship for  $v_x$  as proportional to  $OPP/R$ , while  $V_x$  is proportional to  $V_s.v.R/(OPP.[O_2])$  (where oxygen concentration regulates membrane permeability), or the ratio of the ventricular work per beat / effective osmotic pressure of the plasma proteins times the oxygen concentration of the blood, ( $\propto$  vascular filling,  $R.V_s$ ). The situation is represented diagrammatically in Fig. 1 to 4.

If the momentum outside the vessels is proportional to the momentum inside, then the extra-vascular volume  $V_x$  can act as a repository or store for momentum in the nature of a flywheel, while the energy stored is used to give momentum and velocity to the venous blood when fluid enters the 'venous end' of the capillary from the extra-vascular space.

Cyclical changes in the volume of the extra-vascular circulation (such as may be recorded for example by finger plethysmography; q.v. chap 13 ) depend largely on variations of the linear velocity of blood flow during the cardiac cycle. Linear velocity of arterial blood flow depends on the size of the stroke volume, and also on the increase in linear velocity given to the stroke volume by the force of ventricular contraction to produce systolic arterial blood pressure, and energy proportional to ' $Q.R.L.PR$ ' (equivalent to ' $v.R.\eta$ ' and peripheral resistance). This pressure must be converted to linear velocity of arterial flow through the elasticity of the aortic wall, which absorbs pressure energy, and releases it again as increased linear velocity of flow given to stroke volume which then has energy  $\propto v.PR^2$ , or 'augmented stroke volume', with greatly increased kinetic energy as ' $R^2$ '

appears as 'v', and  $\eta^3 \times L[O_2]$  to overcome vascular filling. The increased linear velocity of flow produces increased extra-vascular fluid volume and energy exchange with effector cells with reduced systolic blood pressure, and cell energy store and reduced R and [lactate].

For linear velocity of flow to be equivalent to  $R^2$  requires factors equivalent to  $[O_2]^2$  to be transferred elsewhere, or applied to other purposes. A factor of  $[O_2]$  provides energy for expansion of the volume of the arterial system at each ventricular contraction; i.e., arterial volume proportional to oxygen concentration. Another factor is applied to overcoming the resistance  $\propto$  passive permeability which retards movement of fluid from the capillaries to the extra-vascular space by increasing pulse pressure to become proportional to peripheral resistance ( $v.L.PR.[O_2] \propto v.R.\eta$ ).

Transfer of two factors each equivalent to oxygen concentration from  $R^2$  allows it to become proportional to 'v', or kinetic energy in place of stored energy from peak arterial pressure ( $R^2.vx$ , with  $vx.[lactate]$  becoming  $\%L.\eta$  or equivalent to stroke volume, which then partially replaces lactate in tissue fluid. In this way aortic elasticity is able to convert pressure energy to flow energy, but only so long as the elasticity of the aorta is maintained.

Fluid enters the extra-vascular space in pulsatile fashion because of variation of linear velocity of flow from arterioles, which occurs as the blood pressure alters from the diastolic to the systolic level, and back again. But evidence of pulsatory linear velocity of flow is lacking in the venules and small veins as fluid leaves the extra-vascular compartment to maintain the venous return. Nevertheless, momentum of blood in these small vessels must be preserved, in order to maintain the venous return at the same volume flow rate as that in the arterioles. Energy must be 'stored' from the systolic part of the cycle to the diastolic portion, in order to even out the flow rate throughout.

*How does this occur?*

It would require expansion of the volume and/or pressure of the tissue fluid, without significant change in the linear velocity of fluid in the extra-vascular compartment throughout the cardiac cycle. This situation is difficult to visualise because of the relationships which must exist between the volume and linear velocity of fluid in the intra-vascular and extra-vascular fluid compartments, where the momentum in each is proportional to that in the other. If 'Vx' is proportional to 'v', then 'Vs' is proportional to 'vx.  $[O_2]$ ', and as 'Vs' is augmented by the stroke volume 'Q' at each ventricular contraction, 'vx' is also likely to vary throughout the same period. This suggests that there must be some 'buffer' mechanism, which absorbs energy as the momentum in the extra-vascular fluid increases, and releases it again steadily to maintain momentum and linear velocity as the blood pressure falls again. Two possible mechanisms present themselves. Energy could be absorbed by the normal elasticity of connective tissue provided by elastic fibres, or by the expansion of cell volume as the wave of kinetic energy forces fluid across the cell membranes. Fluid is then expelled again by the active metabolism of the cells, and this produces an elastic system for

maintenance of motion and momentum. Energy entering the system is pulsatory with local variation of volume, linear velocity, and lateral pressure, but the energy leaves in a 'linear' fashion, with steady volume flow, linear velocity, and lateral pressure, giving rise to a uniform flow in the small veins. In such a case, the energy 'store' can only be maintained by the active metabolism of the cells, and without this metabolic activity, the venous return could not be sustained, and the circulation must fail. Such a system however would provide a more substantial and reliable method of sustaining venous return, than the natural elasticity of connective tissue alone, but it does suggest that satisfactory circulatory function might not simply depend on the activity of the heart acting in isolation, and that it might in addition be dependent on the metabolic activity of other body cells.

Although the linear velocity of the extra-vascular fluid might also vary and have its own effects on the fluid exchange between the cells and the extra-vascular fluid, the effect would be relatively small and difficult to detect in comparison with that of the cell metabolism. The pressure / flow relationship depending on elasticity of the arterial system becomes mirrored in the energy exchange with effector cells ( $\propto v$ ) so that if aortic elasticity increases linear velocity of flow in the vascular system, it also increases energy exchange with effector cells, but without increase in 'vx', which is in fact reduced with oxygen increased while carbon dioxide is reduced as well as pulse rate. Linear velocity of flow increases as 'R' increases with respect to pulse rate, which is limited by the cardio-depressor reflex (Marey). It implies that as aortic elasticity is reduced, more work and arterial pressure is required to maintain energy exchange with effector cells, and this represents one type of 'hypertension'.

If the extra-vascular volume, 'Vx', is proportional to  $V_s.v.R/OPP$ , (where OPP varies with  $[O_2]$ ), while the vascular filling, 'Vs.R' is virtually constant for a particular individual under conditions of rest, then Vx is proportional to 'v', and  $D_x.V_x.v_x$  or  $D_x.V_x.OPP/R$  is the momentum of the extra-vascular fluid. This can then be expressed (even if only approximately) as 'v multiplied by  $OPP/R$ ', or 'v.vx' (assuming a constant value for 'viscosity'). Now the pulse pressure is equal to  $D.v.IPR/2$  and cell 'free energy (I.PR)' is equal to  $R.v_x$ , so v.vx can be expressed as  $PPs/R$ , and this implies that the ratio  $PPs/R$  gives a reasonable approximation of the relative momentum of the extra-vascular (extracellular) fluid for that particular individual; while Vx is approximately  $2PPs/OPP$ , or  $2PPs/IPR$ , and an indication of the relative volume of extra-vascular fluid for the same individual, and proportional to 'v'.

It is recognised that these are only very rough approximations, but they are stated in order to indicate the significance of the relationships which these readily determined parameters, viz. APs, PPs, and PR, might have with each other, and with the extra-vascular circulation.

Before proceeding further, it might be profitable to summarise to some extent certain conclusions which have been reached regarding the mechanics of the circulation which have implications for its normal functions.

1. The work done by the left ventricle per beat is  $\propto V_s.v.R$ , and the balance between kinetic and potential energy is given by the ratio  $v/R$ , which is proportional to  $PPs/APs$ , and virtually

proportional to the momentum in the circulation, and in the extra-vascular compartment (because of the relative constancy of the product  $R \cdot V_s$ ).

2. The volume of the arterial system depends on the relative amount of potential energy developed per beat, and is proportional to the ratio ' $R/IPR$ ' (designated the vascular index) which determines the relative strain imposed on the arteries by cardiac activity, because the arterial system (particularly the elastic arteries) acts as a store for potential energy.

3. The kinetic energy developed by the ventricle per beat, appears as the average mean momentum of the systemic circulation. The mass of blood, ' $D \cdot V_s$ ', multiplied by the average mean linear velocity, ' $v$ ', is the momentum, which can also be represented as ' $D \cdot Q \cdot IPR$ ' (the density of the blood, ' $D$ ', is omitted on many occasions because of its relatively constant value).

4. The volume of extracellular extra-vascular fluid, ' $V_x$ ', is proportional to ' $v_x \cdot v \cdot R / OPP$ ' and approximately to ' $v$ ', because of the relative constancy of ' $V_s \cdot R$ ', which is directly related to ' $OPP$ ' (by  $[O_2]$ ). The relative volume of ' $V_x$ ' is indicated by the ratio ' $PPs/R$ ', while the momentum of the extra-vascular fluid is proportional to ' $v_x \cdot v$ ' (or  $PR \cdot IPR$ ) and is indicated by ' $PPs/R$ '. The average mean linear velocity of the extra-vascular fluid is ' $v_x$ ', which is proportional to ' $OPP/R$ ', ' $R \cdot V_s / [O_2] \cdot R$ ', ' $V_s / [O_2]$ ', or ' $1 / [O_2]^2$ '.

(The relationships between fluid volumes depends heavily on maintaining the ratio between pulse rate and arterial volume at a stable value; i.e., ' $1 \cdot \eta / [O_2]^2$ ' needs to be kept constant. For the most part this is achieved by the cardio-depressor mechanism provided by the cardio-depressor nerves. In general, a slow pulse rate is indicative of an elevated oxygen partial pressure in the 'effector' cells, while an accelerated pulse is associated with a diminished oxygen partial pressure in these cells. The change in pulse rate acts to restore the balance by changing the linear velocity of flow in the capillaries.)

5. The greater the momentum in the extra-vascular compartment, the greater will be the momentum imparted to the venous blood, and this produces a greater venous return in unit time.

6. The efficiency of the peripheral circulation is given by the ratio ' $Q/V_s$ ', or ' $v/IPR$ ' (an increase in stroke volume increases the mechanical efficiency of the ventricle. Sarnoff et al. 1958). The kinetic index, ' $Q/IPR$ ', indicates the proportion of the ventricular energy which appears as flow energy, while ' $V_s/IPR$ ' is proportional to ' $Q/v$ '. (It should also be pointed out that ' $V_x/IPR$ ' is also approximately proportional to the efficiency of the circulation, and this may be referred to in later discussion, particularly the direct relationship between ' $V_x$ ' and ' $IPR$ ' when efficiency and ' $OPP$ ' are constant).

7. As ' $IPR$ ' is the variable which largely determines the energy released by the ventricle per beat, its other relationships should perhaps be mentioned; ' $APs/IPR$ ' is proportional to ' $R$ '; ' $PPs/IPR$ ' is proportional to ' $D \cdot v/2$ '; ' $APs$ ' = ' $R \cdot IPR$ '; ' $PPs$ ' = ' $D \cdot v \cdot IPR/2$ '; the work done by the ventricle per beat  $\propto$

'Q.R.IPR'.

The relationship which exists between extra-vascular extra-cellular fluid volume, 'Vx', and 'IPR', when 'Q/Vs' and 'OPP' are constant, has important implications for the control and maintenance of extra-vascular volume, which it is now convenient to explore further. 'Vx' is closely related to the ventricular work done per beat, and inversely to the osmotic pressure exerted by the plasma proteins. Under ordinary circumstances, when there is little variation in the value of the product 'Q.R', or of 'OPP', 'Vx' will be directly determined by variations of 'IPR'. This suggests that 'Vx' is closely associated with the relative volume of blood in the capillary circulation, which is also related to 'IPR', 'v', and 'PPs/IPR'. The relationship appears because both 'v' and 'PPs' are each directly proportional to 'IPR'.

The extra-vascular volume can then be varied either by alteration of the pulse rate, or by alteration of the circulatory length, 'l', which latter implies variation of the product 'R.Vs' (or  $l^2 \cdot \eta$ ). In general it is alteration of the pulse rate which varies extra-vascular volume, but changes in 'R.Vs' (circulatory filling) which occurs for instance in hypertensive states, can also vary it. It is possible to extend this line of reasoning to determine the factors which influence the volume of fluid within the cells on the one hand and the intra-vascular volume on the other.

Turning first to consider the volume of fluid contained within the tissue cells at any particular time, there are some general observations which need to be made. As with all living cells maintained in a fluid environment, osmotic equilibrium with the environment is an initial condition modifying any further exchanges which may be allowed to occur. Equilibrium involves not only the large protein molecules which the cell contains, but also ions such as sodium and potassium, magnesium, calcium and phosphate, to name some obvious ones, which do not pass freely across the cell membrane under normal circumstances unless certain conditions are met.

Once equilibrium is reached, so that the fluid inside and outside the cell is isotonic having regard to the different ionic concentrations on each side of the cell membrane, there is still one important factor which can vary the equilibrium. This factor is any local change of pressure applied on either side of the cell membrane, to which the other side of the membrane is not subject. For example, should some hypothetical large molecule within the cells be broken up into a number of smaller molecules to which the cell wall still remains impermeable, fluid will enter the cell until osmotic equilibrium is again reached. Again, a certain pressure will exist within the cell which tends to extrude fluid against the pressure present in the tissue space which is at the same time forcing fluid back into the cell, so maintaining equilibrium.

The fluid outside the cell is not at rest, and the lateral pressure which it exerts upon the cell wall will vary accordingly, depending upon the velocity of movement. If the extra-vascular velocity, 'vx', is increased, the pressure outside the cell will fall, and fluid will leave the cell, while if the velocity should diminish, the lateral pressure will increase, forcing fluid back into the cell. Other things being equal, then, exchange of fluid between the cell and the extra-vascular fluid will be greatly influenced by the linear velocity of the fluid in which the cell is immersed. Anything which increases this velocity will extract fluid from the cell, while slowing of the linear velocity of the extra-vascular

fluid will encourage fluid to re-enter the cell (providing of course that the other constituents of the cell and of the extra-vascular fluid have otherwise remained unchanged).

Any alteration in general circulatory activity that varies the linear velocity of the extra-vascular fluid,  $v_x$ , might therefore be expected to alter the fluid content of the tissue cells, independently of any activity of the cell which might also have its own effect upon that cell's fluid balance. The fluid content of the cell will then be subject to alteration by any change in the dynamics of the extra-vascular fluid. For a given value of momentum in the extra-vascular compartment, an increase in  $V_x$  must result in a fall in  $v_x$ , with fluid passing into the cells. Now as  $V_x$  is proportional to the linear velocity of the blood,  $v$ , and momentum is proportional to  $v.v_x$ , any increase in  $V_x$  must be accompanied by an increase in  $R$ , which increases as  $v_x$  falls. This means that as  $R$  increases fluid will pass from the extra-cellular compartment to the intra-cellular compartment, and the ratio relating their volumes will then be proportional to  $R / IPR$ , or the 'vascular index', which is also proportional to  $R / v$ . In a similar way the ratio  $V_s / V_x$  is proportional to  $V_s / IPR$  or  $Q / v$ . The conclusion is that intra-vascular volume is related to extra-vascular volume is related to intra-cellular volume as  $V_s : IPR : R$ , and the volumes of these three compartments of body water are determined by the relative values of the three parameters which together determine ventricular work and circulatory energy. Of the three the most readily variable is the pulse rate, and variations of extra-vascular volume tend to be wider than those of intra-vascular volume and intra-cellular volume in a relative sense.

All fluid taken into the body (excluding that which is produced by metabolic processes) must pass into the vascular tree, and from there to the extra-vascular compartment, and finally into the cells, which are the final areas for storage of body fluid. From there it is drawn upon to replenish the extra-vascular compartment, according to the dynamics of the circulation, and it finally passes to the vascular system before it becomes available for renal excretion. This volume of fluid however is what remains after the skin excretion of water (and salt) during the removal of metabolic heat.

In summary, (assuming a constant value for the viscosity of blood) if the vascular index,  $R / IPR$ , is also the ratio which determines fluid volume of the cells / extra-vascular fluid volume, and  $V_s / IPR$  is the ratio of vascular volume / extra-vascular fluid volume,  $R.V_s / IPR$  or  $L.\eta / PR$ , is the ratio of vascular filling / extra-vascular volume. If  $V_s$  is constant, then  $L.\eta / PR$  will also determine the ratio of cell volume / extra-vascular fluid volume, while if  $R$  is constant,  $L.\eta / PR$  will then determine the ratio of vascular volume / extra-vascular fluid volume. The ratio  $L.\eta / PR$  therefore has a pre-eminent role in determining fluid distribution within the body. The logical conclusion from this line of reasoning is that if the work done by the left ventricle per beat is directly proportional to the extra-vascular fluid volume,  $V_x$ , (and eventually to  $IPR$  if both  $Q$  and  $R$  are relatively constant); while  $Q$  is proportional to  $V_s$ , and  $R$  is proportional to  $V_c$  (the intra-cellular fluid volume); then  $Q / V_x$  is proportional to  $[CO_2] / PR$ ;  $V_c / V_x$  is proportional to  $[O_2] / I.PR$ ; and  $Q / V_c$  is proportional to  $[CO_2].L/[O_2]$ , and so the pulse rate.

The distribution of fluid between the various compartments in the body is then a function of the gas concentrations in the active tissues, and the pulse rate (if one ignores 'apparent viscosity' of the

blood). The most energy efficient situation is then likely to be that in which there are lower values of 'R' and 'IPR', with an increased value for 'Q'. These are the conditions found in 'physical fitness', where while the ratio of Q.R / IPR may be little altered, it is now achieved with increased values for 'Q' compared with 'Vs' (in other words a higher value for L compared with  $[CO_2]$ , and lower values for PR, with viscosity appropriately adjusted, and oxygen maintained through aortic elasticity (see chapter 13).

Volume distribution between cells and blood, depends on the relative values of R and Vs, and the relationship between the two is determined by the ratio between resistance per unit velocity per unit volume, and the systemic blood volume. Within the vascular system, the least requirement for energy to produce fluid movement occurs when the component of lateral pressure distending the vessel walls is just balanced by the linear velocity of flow, and these conditions define the volume of the vessel supplying the particular area.

The volume of the blood vessels depends on v,R and  $\eta$ , which together constitute the peripheral resistance. If R becomes a greater factor in the resistance, and v is relatively reduced, then vascular volume is increased; if R is reduced and v increased, then vascular volume is reduced. These variations are regulated by the osmotic pressure of the plasma proteins, which is directly related to R.Vs, or vascular filling, together with oxygen partial pressure, so that vascular volume becomes related to  $OPP \cdot [O_2] / R$ . The least energy is required when v is proportional to  $R^2$ , and cell volume then depends on  $OPP \cdot [O_2] R / v$ , or  $L \cdot [O_2]$  (cell energy store at diastole)..

Vascular volume depends on the inverse ratio, or  $v/R$ , and the least energy then requires vascular momentum to be proportional to  $Vs \cdot v$ . The ratio between cell volume and intra-vascular volume remains stable only when the values of R and OPP are stable, each depending on the oxygen concentration in cells and tissue fluid, which may vary both cell volume and the permeability of cell and capillary membranes. Volume distribution of body fluid between the three compartments is regulated by variation between v, R, and OPP at systole, (or v, R, and  $\eta$  at diastole).

The significance of the proposed relationship between ' $R^2$ ' and 'v' is that they are both dependent on the dimensions of the effector cells as well as the dimensions of the systemic circulation, the volume and retained energy levels of tissue fluid, and relative concentrations of the respiratory gases. Because linear velocity is proportional to 'R.PR', the ratio 'R/PR'  $\propto [O_2]^2$  represents all of the effector cell dimensions, cell length, cross sectional area, and volume (length, 1/cross sectional area or carbon dioxide concentration, and oxygen concentration, or cell volume) as well as the dimensions of the systemic circulation. The ratio 'R/PR' defines the size and shape of both effector cells and systemic circulation which become inversely related, and change in the ratio alters the relative size of each. For this reason change in the value of the ratio has a profound effect on circulatory activity, and the size and energy content of the main fluid compartments of the body, which need to be kept within strict limits for satisfactory function.

In a previous chapter it was suggested that a close relationship exists between the gas concentrations in the active tissues, and certain parameters in the above relationships, and it is now proposed to explore these more fully.

In essence it was suggested that the evidence pointed to a relationship between the stroke volume,  $Q$ , and the partial pressure of carbon dioxide maintained in the tissues, so that  $Q$  is proportional to  $[CO_2].l$ , and that the diameter of the arterioles is related to the partial pressure of oxygen which has to be maintained in order that the oxidative activity of the tissue can proceed in a satisfactory manner and at a satisfactory rate. If the oxidative activity is not sufficient, products of glycolysis (lactate) accumulate, while if the oxygen partial pressure is raised to a sufficient degree to improve the oxidative activity, constriction of the small vessels occurs.

The oxygen concentration is proportional to  $1/a$  (where  $a$  is the cross sectional area of the vascular bed expressed as an average mean equivalent) and the resistance per unit velocity,  $R$ , is then proportional to  $[O_2].l.\eta$ .

It is now possible to transfer these values into the previous relationships, namely those involving  $Q$ ,  $R$ ,  $v$ , and  $V_s$ , so that  $v$  becomes proportional to  $[CO_2].[O_2].l.PR$ , while  $V_s$  is  $l / [O_2]$ . The ratio  $Q/V_s$  is  $[CO_2].[O_2]$ , and  $Q/R$  is  $[CO_2] / [O_2].\eta$  (the metabolic index; vide infra). This is also the ratio of momentum / systolic arterial pressure. Momentum will be proportional to  $[CO_2].l^2.PR$ , and APs to  $[O_2].l^2.\eta.PR$ , while PPs is proportional to  $[CO_2].[O_2].l^2.PR^2.D/2$ .

The ratio  $v/R$  can be represented as proportional to  $[CO_2].PR / \eta$ , while  $v/Q$  is proportional to  $[O_2].PR$ . The purpose of listing these relationships, is that it allows one to predict the effect that any change in gas concentration in the tissues overall is likely to have on the main parameters which are of importance in the circulation. They can also be illuminating in the consideration of gas transport regulation, and its effect on the extra-vascular circulation and venous circulation. For instance the volume of the extra-vascular fluid,  $V_x$ , is proportional to  $[CO_2].[O_2].l.PR$ , while the total of oxygen transported for oxidation in unit time will be proportional to the cardiac output per second,  $Q.PR$ , or  $[CO_2].l.PR$ . The quantity of oxygen which the tissues use, on the other hand, depends on the oxygen tension which has to be maintained for efficient oxygenation to take place. The higher the oxygen tension which is required, the greater the resistance per unit velocity which is offered to the circulating blood, i.e., 'R', because 'R' is proportional to ' $[O_2].l.\eta$ ', and systolic pressure varies as a consequence of variation of the value of 'R'. Because of the implied difficulty in maintaining satisfactory oxygenation, accumulation of the products of glycolysis occurs more readily, in the manner which has previously been indicated. (Chap.6). For maximum transport and delivery of oxygen, maximal conditions for its utilisation are necessary, so that the capacity to utilise oxygen at lowered partial pressure with the production of carbon dioxide and without accumulation of excessive amounts of the products of glycolysis are the essential features. While the production of carbon dioxide is a requirement for the maintenance of adequate stroke volume, the amount of oxygen delivered per unit stroke volume is a function of pulse rate, and the oxygen concentration

which it is necessary to maintain in the tissues for satisfactory usage of oxygen to be achieved. If the oxygen level for adequate oxygenation is low, much larger quantities of oxygen can be delivered, than when the oxygen concentration needs to be increased. A larger oxygen concentration leads to a larger value for 'R', with restriction of blood flow in the area unless the perfusion pressure is raised. The result is that an adequate amount of oxygen can only be supplied at the required partial pressure, if there is an increase in systolic arterial blood pressure, 'APs'. The acceleration of the pulse rate, together with increase in blood pressure which occurs at the onset of activity, leads to an increase in the partial pressure of oxygen at the local tissue level, but if the tissues can use oxygen at a lower partial pressure, increased delivery of oxygen will occur as the partial pressure falls, so that the activity can be maintained, without the initial blood pressure elevation being maintained for the full duration of the activity. It can only occur if the conditions for oxygen utilisation remain adequate. Should a high level of oxygen concentration be functionally necessary, blood flow to the area will be more restricted, and a higher systolic blood pressure will be necessary for the duration of the activity. A rise in the products of glycolysis may also occur, which in turn may lead to a further prolongation of the rise in systolic arterial pressure, in the way that has been mentioned in a previous chapter.

At the same time, the systemic blood volume,  $V_s$ , is proportional to  $1 / [O_2]$ , and is therefore restricted whenever the general level of  $[O_2]$  in the tissues rises, while the stroke volume, 'Q', is limited whenever  $CO_2$  production is restricted and  $[CO_2]$  falls. The ratio  $Q/V_s$  is then reduced; i.e.  $[CO_2].[O_2]$  and  $v$  are also less, which implies that both  $V_s$  and  $V_x$  are both limited when the oxygen concentration required for efficient oxygenation in the tissues is required to rise, though this limitation is modified by 'l.PR', which affects each of these volumes differently. With a rising oxygen tension in the tissues, momentum in both the circulation and the extra-vascular fluid falls, and the velocity of blood in the venous system (venous return) is diminished. The circulatory rate then diminishes as the oxygen partial pressure in the tissues overall begins to rise. The circulatory rate, on the other hand increases as the oxygen tension falls, provided only that oxygen consumption is not hindered as a result of the fall in oxygen partial pressure, so that carbon dioxide production is not disturbed, and there is no accumulation of the products of glycolysis.

Under these latter circumstances momentum in both the vascular system and the extra-vascular fluid increases, while this momentum is transmitted to the venous blood, with increase in the velocity of venous flow and venous return to the heart. Continuation of the life process requires continual transfer of fluid and energy between fluid compartments, and is accentuated if the differences in energy and volume are increased by pulsatory flow, which becomes a significant factor in circulatory activity requiring improved performance.

There are of course other important effects of changes in the partial pressure of oxygen on the peripheral circulation, not the least of which is an observable change in capillary permeability with falling oxygen tension. Because of this effect, capillary permeability increases towards the 'venous end' of the capillary, although the permeability change can be reversed by changing the direction of

blood flow, so that blood in what was originally the 'arterial end' is now more reduced with a lower oxygen tension than that in the original 'venous end' of the capillary. The result is that the partial pressure of oxygen in the tissues can have a considerable bearing on the apparent effective osmotic pressure of the plasma proteins, and influence the values of  $V_x$  and  $v_x$  in the extra-vascular space, in comparison with those of  $V_s$  and  $v$ . In general, while  $V_x$  and  $v_x$  increase with increased tissue activity, and with increase in oxygen utilisation at a lower oxygen tension, both  $V_x$  and  $v_x$  are decreased as the oxygen tension rises. When the ventricle fails and oxygen tension in the tissues falls (but without adequate oxygen utilisation occurring) this increase in the volume of the extra-vascular fluid can reach embarrassing levels, with the occurrence of oedema, and slowed venous return, producing a slowed circulation rate, cyanosis, and so on.

The extra-vascular circulation becomes possible because of changes in the dynamics of flow produced in the system of elastic arteries following discharge of stroke volume from the left ventricle to produce 'peak arterial filling'  $\propto R.L.PR$ . Vascular distention,  $\propto$  oxygen concentration in arterial blood, is resisted by the elastic properties of the aorta and other elastic arteries, and the oxygen concentration becomes 'stored' or 'fixed' to maintain the distention proportional to the oxygen concentration available. The greater the aortic distention, the greater the concentration of oxygen required to maintain it. To keep the concentration to a minimal level requires aortic elasticity of sufficient degree able to reduce oxygen needed to be reserved for this function (and so the oxygen load and lactate concentration) to be assumed by ventricular function for each beat. The increase in oxygen above that required for other functional and metabolic activities, becomes a fixed load the ventricle must accept for each beat, and it can only be reduced by increased aortic elasticity with distention reduced to a lesser value. (oxygen is of course required for metabolism of pyruvate to produce carbon dioxide, as well as for survival of effector cells, where accumulation of  $[O_2]^2$  is needed to be present at all times to keep them viable and maintain the volume and energy level available to them and preserve passive permeability. Increased oxygen is also necessary to allow oxidative phosphorylation to produce high energy phosphate bonds and increase cell energy when the oxidative enzymes associated with 'Kreb's cycle' are otherwise inhibited by higher than desirable oxygen levels. These functions need oxygen levels which need to be met for function to continue.) Limiting aortic distention allows oxygen load, which must otherwise be stored in the aortic wall, to be reduced with greater elasticity, and allows a nett saving of ventricular energy through limitation of arterial volume and oxygen load per beat. If the aorta is not distended, ventricular energy appears as increased linear velocity of flow rather than as systolic arterial pressure, to be later converted to linear velocity by reduction of 'R', through transfer of oxygen by increased aortic volume, but requiring increased ventricular work to move additional oxygen per beat, related to the increased volume. The increase in linear velocity of flow results in augmented stroke volume and increased extra-vascular fluid volume. Some oxygen is still 'stored' in the aortic wall as  $R^2$  is converted to 'v', but much of this oxygen is 'wasted' in the sense that it is released at the arterioles to increase constriction and limit linear velocity of flow and tissue fluid volume, though oxygen to convert 'v<sub>x</sub>' to ' $\eta$ ' as fluid returns to venous blood is still required. Increased aortic elasticity reduces the restriction of tissue fluid volume depending on oxygen concentration. The extra linear velocity of flow with limitation of oxygen stored in the aortic wall, both assist in the production of tissue fluid, and the extra-vascular circulation. As the latter is increased, peripheral resistance is reduced, with

less oxygen to constrict arterioles, and reduce permeability of the capillary membrane.

In order to emphasise the considerable importance of the time element in cardiac muscle contraction upon the efficiency of the muscle to do mechanical work, the time relationships can be summarised as follows.

1. The maximum pressure developed in the ventricle during the phase of isometric contraction is equal to the diastolic blood pressure (DP). This can be represented as the product of ventricular end-diastolic pressure and the contractility factor ( $EDP \cdot \lambda$ ). Ventricular end-diastolic pressure results from the product of 'R', the resistance per unit velocity offered by the circulation to each ml. of blood, and 'LTDTR', the ratio of initial fibre length / time taken for the development of unit isometric pressure in the ventricle from the initiation of the contraction, i.e. diastolic pressure is proportional to ' $\lambda \cdot R \cdot \text{initial fibre length} / \text{time taken to develop unit isometric pressure}$ '. (DP is proportional to  $\lambda \cdot R \cdot LTDTR$ )

2. Once the isometric pressure developed equals the diastolic blood pressure, the aortic valve opens, and further contraction then results in further rise in pressure, and in the ejection of blood into the aorta (the stroke volume) while the pressure rises to peak systolic pressure. The ejection phase therefore involves both muscle shortening, and the development of a further increment in ventricular pressure, equivalent to the pulse pressure. Development of increased pressure in the ventricle involves energy production, but this is potential energy only, and no work is done until movement of the blood occurs, so that kinetic energy appears, and it is at this stage that the concept of mechanical efficiency of the ventricle appears. The development of potential energy nevertheless requires the utilisation of oxygen. If Starling's Law is valid, this oxygen usage will be determined by the initial length of the muscle fibres, and modified by the capacity for contraction by the environmental considerations which are incorporated in the contractility factor, ' $\lambda$ ', and a factor ' $R / \text{contraction time}$ ', which is in essence the loading necessary to produce a particular speed of contraction. The oxygen consumption then is calculated as proportional to ( $R \cdot \lambda \cdot \text{initial length of cardiac fibres}$ ), or tension developed times contraction time, so that the greater the duration of the contraction, the more oxygen is used for a given fibre length in order to maintain a given developed tension.

3. Considering only the oxygen required for the development of potential energy, there will be two quantities involved.

a. Oxygen required for isometric contraction and development of peak isometric tension, 'DP', which is ' $\lambda \cdot R \cdot \text{initial fibre length} / \text{duration of contraction}$ '.

b. Oxygen required to develop and maintain further tension during the ejection phase. This is the systolic pressure, and the oxygen required to develop and maintain this extra pressure will be ' $\lambda \cdot R \cdot \text{initial fibre length} / \text{duration of the further period of contraction}$ '.

4. The total oxygen required for the development of the final peak systolic tension, AP, will include that required for the production of diastolic pressure, DP, plus that required for the production and

maintenance of AP, or  $\lambda \cdot R \cdot \text{Initial fibre length}$  (1/time for isometric contraction,  $T_d$ , + 1/time for further development of systolic pressure,  $T_p$ ). That is  $\lambda \cdot R \cdot \text{Initial fibre length} \cdot (T_d + T_p) / (T_d \cdot T_p)$ .

This can be compared with Sarnoff's T.T.I (tension time index) where the product of the mean systolic pressure and the duration of systole was found to correlate well with the oxygen consumed per beat. In this assessment  $R \cdot \lambda \cdot \text{Initial fibre length}$  is regarded as proportional to 'peak systolic pressure multiplied by  $T_d \cdot T_p / (T_d + T_p)$ ', and also to the oxygen consumed per beat, but no allowance has been made for the oxygen consumed by shortening of the muscle fibres during the ejection phase.

Once shortening commences, external work is done. In general the longer the ejection phase, the greater the amount of blood which is expelled per beat (the stroke volume,  $Q$ ). The ventricular work done per beat is  $Q \cdot APs$ , while the oxygen consumed will be the sum of the oxygen consumed during isometric contraction, ( $Dps \cdot \text{duration of isometric contraction}$ ), and the oxygen consumed during the ejection (shortening) phase, which will be proportional to ' $APs \cdot \text{duration of ejection phase}$ '. Now the same oxygen usage could occur with a high APs and small duration of ejection phase, as with a lower APs and a more prolonged ejection phase, but in the former case, the turnover of energy requires to be much faster than in the latter, so the power developed for the same amount of work done is accordingly greater. This means that ventricular contraction is mechanically more efficient with a longer ejection phase, and a moderate developed tension, or in other words with a larger stroke volume rather than a higher systolic blood pressure. The requirement then is for a rapid isometric contraction followed by a more prolonged ejection phase, and the mechanical efficiency can be varied by altering the ratio between the duration of the two phases.

This normally involves either a variation of stroke volume with respect to total circulating blood volume, or reduced initial fibre length, and/or the time taken for isometric contraction, both of which are usually accomplished by variation in ventricular end-diastolic pressure (EDP). As end-diastolic pressure can be represented by  $R \cdot LTDTR$ , variations in either of these will achieve the same result, as will changes in the contractility factor,  $\lambda$ .

Synchronous fluctuations of the volume of the extra-vascular fluid accompanying the arterial pulse. If the level of momentum in the circulating fluid in the body is proportional to  $v / R$  (average mean linear velocity / resistance per unit velocity for each ml. of blood in the systemic circulation) any rapidly occurring changes in momentum will depend on rapid changes in linear velocity of flow.

It is the 'average mean' value representing these rapidly varying values which is used to calculate the 'average mean' momentum, and it is the variation in this value which brings about changes in the ratios of volumes in the three fluid compartments of the body viz.  $V_x/V_c$ , and  $V_s/V_x$ . While resistance per unit velocity appears to remain relatively constant over the duration of each heart beat, the linear velocity is continuously variable, and changes proportionately with the pressure changes characterising the passage of the pulse wave, so that momentum in a particular area will also vary with changes in linear velocity, which therefore initiate rapid fluid interchange between the various fluid compartments. Although  $v_d$  is a mean figure representing the overall linear velocity of blood in the systemic circulation at diastole, and  $v$  is the 'average mean' linear velocity representing an

overall value of the linear velocity of blood in the systemic circulation, the linear velocity in a particular area may vary widely outside these limits, especially with the passage of the pulse wave into the area. These rapidly changing velocities result in rapidly changing volumes, and the interchange of fluid between areas, but the overall fluid volumes in each compartment will depend on the ratios of the average mean values of  $v/R$  and/or  $Q/v$ , combined with the osmotic pressure exerted by the plasma proteins.

The fluid exchange between the extra-vascular compartment and the cells, and between the extra-vascular compartment and the circulating blood is therefore pulsatile, and allows the storage of energy in the extra-vascular compartment which is in turn responsible for the 'flywheel' effect which later allows energy and fluid transfers back into the cells and circulation following systole. As the pulse wave reaches a particular area, extra fluid leaves the blood from the small vessels, and passes to the extra-vascular space, increasing both volume and momentum in this compartment.

Momentum in the intra-vascular compartment is related to both volume and linear velocity ( $V_s.v$ ), and also to the momentum in the extra-vascular space ( $V_x.v_x$ ), and as  $V_x$  is proportional to  $v$ ,  $V_s$  is proportional to  $v_x$ . As  $V_s$  increases so does  $v_x$ , but increased  $v_x$  leads to decreased  $V_c$  (because ' $v_x.R$ ' is proportional to ' $OPP$ ', and ' $v_x$ ' can only increase if ' $R$ ' is reduced, i.e., ' $V_c$ ' is reduced).

With the pulse wave then, local vascular volume and extra-vascular volume increases but intra-cellular volume might be expected to fall, with the increased extra-vascular volume being produced by contributions from both intra-vascular and intra-cellular volumes. Nevertheless, any increase in ' $V_s$ ' and /or ' $V_x$ ' is likely to be shortlived or even negligible, because the expulsion of stroke volume by the ventricle is followed by rapid loss of fluid to the extra-vascular space, and to rapid ventricular filling, so that vascular volume is unaltered, despite minor alterations of local volume of blood vessels, with variation of linear velocity of flow during passage of the pulse wave. At the same time, the local increase in linear velocity of flow, while it increases flow of fluid to the extra-vascular compartment, also increases the flow to the intra-cellular compartment proportional to ' $v/R$ ', and unless there is some variation of ' $R$ ', any extra fluid passing to the extra-vascular fluid with increase in ' $v$ ', is soon transmitted to the intra-cellular compartment in turn. Linear velocity of the extra-vascular fluid, ' $v_x$ ', will only be altered if ' $V_s$ ' increases with respect to ' $v$ ', or in other words, if the intra-vascular volume, ' $V_s$ ', is increased relative to ' $V_x$ '. For the most part, linear velocity of flow in the extra-vascular fluid, ' $v_x$ ', is unaltered, and the transient alteration in momentum is confined to any small alteration in volume, ' $V_x$ ', of the extra-vascular fluid, while the extra fluid is moving to the intra-cellular compartment, and as a result, ' $V_s/V_x$ ' remains unaltered.

After the pulse wave has receded the passage of fluid is reversed, fluid leaves the cells and passes to the extra-vascular space and then to the intra-vascular compartment as the local linear velocity of flow diminishes again towards the diastolic value, ' $v_d$ '.

This means that when ' $Q$ ' is large compared with ' $IPR$ ',  $V_s$  is reduced with respect to  $V_x$  and  $V_c$ , while  $v_x$  is increased with respect to  $v$ , and consequently the fluid exchange between cells and extra-vascular fluid (and between cells and blood plasma) requires less energy and is more 'efficient' than when  $IPR$  increases with respect to  $V_s$ . The 'notional' efficiency of the systemic circulation as a whole then depends on the expansion of vascular volume per beat as a fraction of that vascular

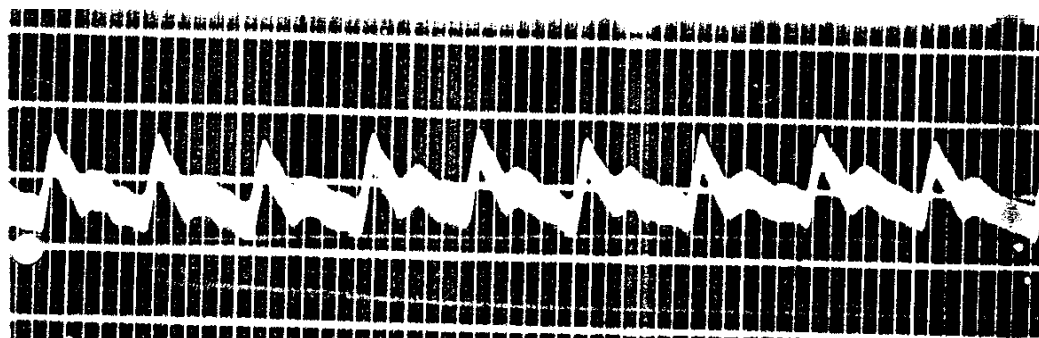
volume i.e.  $Q / V_s$ . The prerequisite is a lower value of 'R', i.e., a lower partial pressure of oxygen at which efficient oxygenation and carbon dioxide production can take place, or in other words when  $Q$  or  $Q/IPR$  are increased. The amount of fluid interchange between cells and extra-vascular fluid depends on the rate and amount of variation in the linear velocity of the extra-vascular fluid produced by each pulse wave, which in turn, is determined by the percentage increase in intra-vascular volume presented to that particular area per beat. For the systemic circulation as a whole this is the ratio  $Q / V_s$ . While this ratio is unaltered, linear velocity of flow in the extra-vascular circulation remains constant, and any change in momentum in this area is reflected in the volume of the extra-vascular fluid. The mechanism which limits variation of 'vx', involves the relative stability of the osmotic pressure exerted by the plasma proteins, so that 'vx' is constant while 'OPP/R' is also constant. By limiting the value of linear velocity of fluid in the extra-vascular compartment, and confining changes in momentum to changes in volume between the main fluid compartments, the osmotic pressure of the plasma proteins, acts as an important regulating mechanism, relating volume flow with arterial pressure for the region.

It has already been argued (CHAPTER6) that the concept of 'vascular filling' is not simply a question of vascular volume alone, but also includes an element of distention of the vascular walls. For this reason it involves energy exerting force on the vessel walls. This energy is equivalent to the resistance per unit velocity offered to each ml. of blood, and vascular filling is then represented by the product of resistance per unit velocity and the volume of blood in the circulation, or  $R \cdot V_s$ . The energy required to be present in the circulation per beat is proportional to the product of vascular filling and the energy released by each ventricular contraction, which is proportional to  $I.PR$ . The energy present in the systemic circulation per beat is then proportional to  $R \cdot V_s \cdot I.PR$ , or  $APs \cdot V_s$ , and this is the energy required to maintain fluid distribution between the blood, the extra-vascular extra-cellular fluid, and the intra-cellular fluid, or in other words  $V_s \cdot V_x \cdot V_c$  (which can be represented as  $V_s \cdot I.PR \cdot R$ ). At the other end of the energy requirement is the minimal energy which must remain in the circulation at diastole, firstly to ensure sufficient venous return for ventricular filling, and secondly to maintain the energy required for vascular filling, and the linear velocity of blood flow at diastole. The energy required to ensure ventricular filling is proportional to the circulating volume ( $V_s$ ), and the venous pressure ( $VP$ ), while the energy required to maintain vascular filling and linear velocity at diastole is  $vd \cdot R \cdot V_s$ . This gives the equivalent  $Q \cdot DP_s$ , and ventricular efficiency at this minimal level is the ratio of work done to minimal energy required, or  $Q \cdot DP_s / (V_s \cdot VP)$ , as previously stated. In the present derivation however, the value of 'VP' appears to be equivocal, insofar as it would appear to be 'VPs' which is involved, rather than 'VPP' used in the previous formula. In effect, the interposition of the pulmonary circulation diminishes the minimal energy release required by the left ventricle by providing any extra energy needed to increase the value of 'VPs' to that of 'VPP', and in this way right ventricular contraction may improve the efficiency of the systemic circulation. Because energy is retained in the circulation from one beat to the next, production of energy by the ventricle is accordingly reduced from that required ( $V_s \cdot APs$ ) by the ratio  $VPP/DPs$ . Two possible values for efficiency can therefore be calculated; a. the 'notional' efficiency of the circulation, or energy released into the circulation per beat / energy required to be present per beat ( $Q \cdot APs$ ) / ( $V_s \cdot APs$ ) or  $Q/V_s$ , and b. the mechanical efficiency of the left ventricle, or energy released into the circulation per beat / energy produced by the left ventricle per beat, i.e.,  $(Q \cdot APs \cdot DP_s) / (V_s \cdot APs \cdot VPP)$  or  $Q \cdot DP_s / V_s \cdot VPP$ .

Because the ratio of DPs/APs can also be represented as  $v_d/v$ , the energy which must be produced by the ventricular contraction per beat can also be expressed as  $V_s.VPp.v/v_d$ , or necessary minimal energy  $.v/v_d$ . As the extra-vascular volume is a function of the linear velocity, the variations of linear velocity which occur during systole as the velocity increases from a mean figure represented by  $'v_d'$ , to an average mean value of  $'v'$ , before falling again to its original value, would imply that the extra-vascular volume increases and decreases during the cardiac cycle, and that the kinetic energy 'stored' in the extra-vascular and/or intra-cellular compartments varies in a corresponding manner (the "flywheel effect" of storage of kinetic energy). This ebb and flow of extra-vascular volume with associated changes in linear velocity of flow, ensures rapid turnover of fluid in contact with the tissue cells, and also maintains rapid equilibrium of composition between the intra and extra-vascular fluid. As already pointed out, the rapid return of fluid to the intra-vascular compartment, augments the venous volume and velocity, and hence the venous return. In this way the ratio of velocities which largely determines the energy which the ventricular contraction must supply per beat, in order to achieve and maintain fluid balance, also determines the magnitude of the fluid exchange between the compartments per beat (an effect which can be further augmented by increasing the pulse rate).

In summary, contraction of the ventricle increases the linear velocity in the circulation, and expands the volume of the extra-vascular space, and as this linear velocity within the circulation falls again, the extra momentum in the extra-vascular space is transferred along with the extra volume back into the venous circulation and increases venous return. Associated changes in cellular volume (though slightly out of phase with the above) also accompany the variations of extra-vascular volume.

Momentum is proportional to  $V_s.v$ , to  $v/R$ , and to  $Pps/APs$ . Any increase in the ratio  $PPs/APs$  therefore indicates not only an increase in extra-vascular volume, but also increased potential for fluid exchange between the extra- and intra-vascular fluid compartments. What is present then is an equilibrium of fluid balance between the cells, the extra-vascular space, and the intra-vascular compartment, which is continuously varied with variations of the linear velocity of fluid flow during the cardiac cycle. It would be a valuable confirmation of this interpretation, if it was possible to demonstrate these volume changes experimentally. Volume changes in the tissues are best demonstrated with a plethysmographic technique, but in order to record rapid changes, the instrument must have as little inherent inertia in the system as it is possible to obtain. A suitable instrument in this regard is the finger plethysmograph introduced by Goetz (1948). With the use of a similar instrument it is possible to record rapid volume changes in the finger during the cardiac cycle.?



*Figure 9.1.*

*Plethysmographic record from the finger in a normal adult. The record of volume changes is considered to reflect the alteration in momentum per beat, and the energy and volume changes which occur as a result, between the extra-vascular fluid and the cells. Because of the parallel changes in the energy balance which must take place during the cardiac (energy and fluid exchange) cycle, it also gives an indication of the energy and volume changes taking place within the cells. This means that such records may reflect both cardiac and cellular activity, and in this way they are able to 'open a window' into the activity of the cell, without direct interference. The opportunity to observe cellular fluid and energy exchange, and by implication, cellular activity, has not been further explored to date (but refer chapter 11.).*

*Fig.9.2 and 9.3 illustrates the alteration in the shape of the volume changes during the cardiac cycle in the finger of a child, before and after surgery to close a patent ductus arteriosus. This procedure results in changes in the dynamics of the arterial system, as well as that of ventricular ejection. The resultant changes in linear velocity of flow, are reflected in the volume changes in the finger. The problem with interpretation is whether these changes represent changes in volume within the blood vessels, or within the extra-vascular space. The likelihood is that it represents changes in distribution of extra-vascular fluid, rather than expansion of blood volume solely within the vascular system. The rise and fall of volume is so rapid that it would require a much greater change in linear velocity of flow through the capillaries (should the volume changes be confined to the blood vessels only) than would appear likely. The probability is that the increased volume is in the extra-vascular space, and/or tissue cells, largely bypassing the capillary network.*

*The increase in linear velocity in the capillaries which the increased volume flow would require, would involve an increase in perfusion pressure of some magnitude, and/or very rapid changes in vascular resistance during the cardiac cycle with resulting changes in stress on the walls of the smaller vessels accompanying change in vascular filling. Such*

*an explanation is difficult to accept in view of the energy equivalents which have been put forward. If extra-vascular volume is proportional to ventricular work, and inversely proportional to the effective osmotic pressure of the plasma proteins ( $v.Vs.R/OPP$ ), this represents average mean linear velocity times vascular filling / effective osmotic pressure of the plasma proteins. Vascular filling ( $R.Vs$ ) is proportional to the 'apparent viscosity' and the square of the average mean length of the circulation. If apparent viscosity and effective osmotic pressure of the plasma proteins remain unchanged, vascular filling can only change if the average mean length of the circulation is altered, otherwise any change in average mean linear velocity is directly reflected in extra-vascular volume. If the average mean length of the circulation is unaltered, any change in vascular volume must mean a change in the cross sectional area of the vascular bed, which is reflected by an equal and opposite reduction in resistance per unit velocity. These considerations make it likely that any change in the volume of the tissues largely reflect changes in extra-vascular volume.*

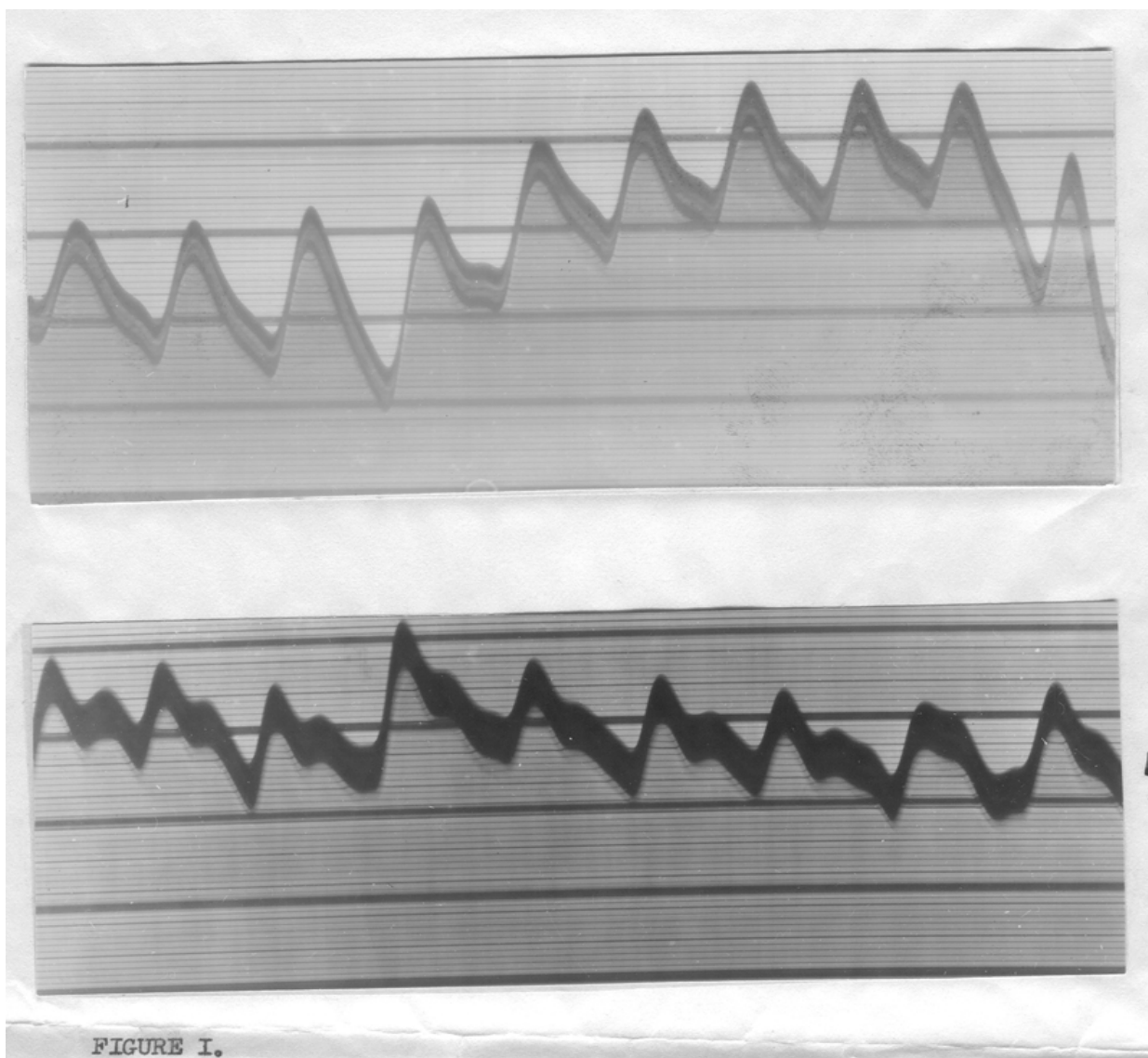
*The tissue volume changes during the cardiac cycle are therefore considered to reflect;*

- a. Changes in linear velocity of flow in the vascular system;*
- b. Changes in the volume of the extra-vascular compartment , and/or cellular compartment.*

*If variations in the pulse volume flow of the finger plethysmograph represent changes in intracellular volume per beat, it also indicates relative stroke volume entering and leaving the cell together with energy exchange during the period. The anacrotic limb of the record then represents the product of stroke volume times permeability of the cell wall ( $\propto [O_2]$ ), or  $\propto Q \cdot [O_2]$ , which is equivalent to 'R'. The dicrotic limb represents energy accumulated within the cell,  $\propto 'l'$  times the rate at which fluid leaves the cell  $\propto 'vx'$ , which is equivalent to 'PR . R', or 'v', representing the energy exchange per beat. The slope of the anacrotic limb indicates the rate at which fluid enters the cell (related to the increase in linear velocity given to circulating fluid by each ventricular contraction, or 'l' , which is the 'slope of the record' and becomes more acute as 'l' increases) .*

*The slope of the dicrotic limb represents the rate at which fluid leaves the cell and is proportional to pulse rate, or 'l.vx'. The increment in linear velocity given to circulating fluid by ventricular contraction times the pulse rate is equivalent to 'l.PR', or free energy within the cell, while the energy increase  $\propto 'R'$  times 'PR' is energy equivalent to 'v', the average mean linear velocity of flow, or energy exchange with the cell. Increasing the slope of the anacrotic limb represents increased increment of linear velocity of flow from ventricular contraction, while increasing the slope of the dicrotic limb is associated with increasing pulse rate.*

*Anything which changes the intra-vascular pattern of linear velocity during the cardiac cycle, changes the pattern of the extra-vascular volume, e.g., the changes in volume pattern which occurs following repair of a patent ductus arteriosus illustrated in Fig.9 (2 and 3).*

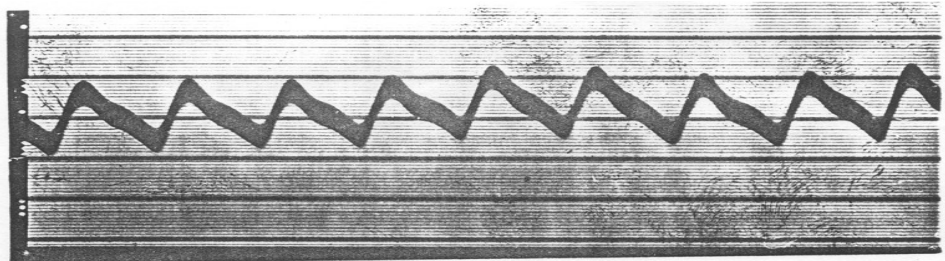


**FIGURE I.**

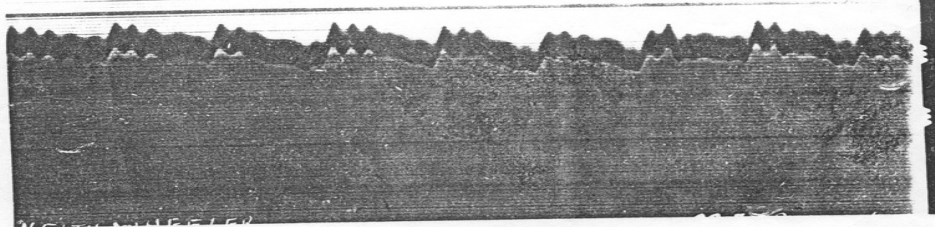
Plethysmograms from the index finger of a boy aged five years, before and after ligation of a Patent Ductus Arteriosus.

- a. Before ligation. (3.4.52). The anacrotic limb is long relative to the total duration of the cardiac cycle and the dicrotic notch is practically absent.
- b. One week after ligation. (10.4.52). The anacrotic limb is now shortened relative to the total duration of the cardiac cycle and the dicrotic notch is more pronounced.

(The thick horizontal lines represent a volume change of 10 mm. No time markings are shown but the records were taken at the same speed in each case).



*Figure  
9.2 and  
9.3*

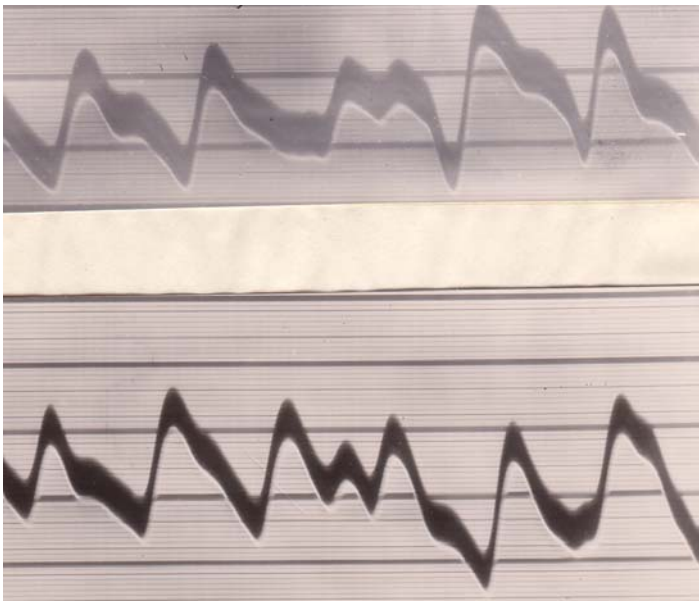


*Plethys-  
mograph-  
ic  
records  
from the  
fingers  
of two  
boys,  
each  
with  
patent*

*ductus arteriosus, showing the typical flow patterns which occur in this condition. The duration of the 'anacrotic' limb is prolonged as a fraction of the total cycle, while the dicrotic notch is virtually absent. The nett duration of inflow into the cells is prolonged, and that of nett outflow is shortened, and with these changes, the nett time for generation of 'free' energy within the cell is increased, compared with the time for expulsion of fluid*

*b 'active' permeability, which latter is still decreased compared with the time for energy 'storage'.*

*The ratios involving 'R', 'Q', and 'L.PR', are then likely to be disturbed, together with the pattern of cellular activity which this requires. Ordinarily, the inflow/outflow rate for the cells is a function of both 'passive' and 'active' permeability, and it therefore reflects the oxygen using capacity of the cells, by the relationship between the duration of the anacrotic and dicrotic limbs of the volume flow curve.*



*After surgical closure of the patent ductus, the flow pattern is altered in each case, with shortened inflow and longer outflow of fluid from the cells, and suggesting a different pattern of activity as a result. The difference between the two records, (i) & (ii), after surgical closure of the ductus, indicated that cellular activity may be altered more radically in one case than in the other.*

*The principle of the finger plethysmograph, in the opinion of the author, represents the most convenient method of demonstrating changes in linear velocity, and extravascular volume, which seem to be available using limited, non-invasive technology. For the sake of interest a plethysmograph from the finger of an eight year old girl admitted for surgery for a presumed patent ductus arteriosus is also shown. Fig.9.4.*

Figure 9.4

*Plethysmographic record from the finger of a girl aged 8 years, considered clinically to have a patent ductus arteriosus, but not exhibiting a typical plethysmographic record. At operation, the only abnormality found, was deficiency in the pericardium in the region of origin of the great vessels. This record is reproduced out of interest concerning the function which has been allotted to the pericardium in the control of ventricular filling and stroke volume. The irregular contributions to fluid and energy exchange which produced this pattern, reflects the irregular alterations in heart size and shape, which are able to occur with an incomplete pericardium.*

*The plethysmograph does not have the typical features present in patent ductus, insofar as there is no increase in the relative duration of the anacrotic limb of the volume pulse. Instead there is an irregularity of the pulse rate together with variation in the volume of the pulse flow. At operation the only finding was a deficiency in the pericardium over the origin of the great vessels. In view of the effect of pericardial resistance on stroke volume and pulse rate which were outlined in Chapter 5, variations in pulse rate and stroke volume could be expected to occur when there was some unevenness in the restrictive activity of the pericardium as in this case. Sinus arrhythmia which is associated with respiratory activity could also mirror changes in this restrictive function. Also illustrated is a recording from a fit male subject, which demonstrates the effect of aortic elasticity in limiting the size of the volume changes recorded, and the slope of both limbs or limitation of energy exchange by restriction of both 'R' and 'PR' to minimum values (Fig.9.1).*

*When vascular filling is increased by increase in resistance per unit velocity (R), there is some constraint placed upon the maintenance of blood volume, which tends to be reduced as 'R' increases because of the reduction of the cross sectional area of the vascular bed. If the reduction of blood volume should continue, eventually stroke volume will also be reduced.*

Vascular filling needs to be sustained so that ventricular filling (Q.R) is also maintained. There are two mechanisms which act to maintain vascular volume. Any rise in oxygen concentration decreases capillary permeability, and the production of extra-vascular fluid. Also as 'R' increases, end-diastolic pressure in the ventricle is increased, with cooling and alteration of liver metabolism, and an increase in the level of plasma protein. These mechanisms together prevent the reduction of Vs below a critical level for maintenance of

stroke volume. If vascular volume is maintained at a relatively constant level, vascular filling will be a function of the value of 'R' (or apparent viscosity, vascular length, and the partial pressure of oxygen maintained in the tissues), and the effective osmotic pressure of the plasma proteins. Should Vs remain at a fairly constant level, changes of Vx and Vc must depend on variations of 'lPR' and/or 'R', i.e., on the systolic arterial pressure. At the same time capillary permeability increases when Vs or vx are increased, while it will be reduced with reduction in Vs and/or vx .

Vascular filling can be represented as R.Vs, equivalent to length squared times 'apparent' viscosity, and its physical dimensions are those of momentum (the dimensions of viscosity are M/L.T, so those of vascular filling are M.L.L/L.T , or M.L/T). 'Vascular filling' could then represent the momentum which is required to maintain the volume ratio between the cells, 'R', and the intra-vascular volume, 'Vs'. Because the intra-vascular volume varies throughout the cardiac cycle by an amount equivalent to the stroke volume, 'Q', the amount of momentum 'exchanged' between the intra-vascular circulation and the cells per beat would be equivalent to 'Q.R', or 'ventricular filling' (which is R.Vs times Q/Vs). This represents the 'stored' momentum exchanged between the cells and the intra-vascular circulation per beat, and is that contributed to the venous circulation to maintain the venous return (and therefore ventricular filling) with each beat. It also represents the momentum accompanying the fluid which enters the cells from the extra-vascular fluid, and is 'stored' in the cells temporarily until returned later in the cardiac cycle on its way to the venous system. The nature of this storage mechanism is obviously of considerable interest, because of the alterations to cellular metabolism, in which it must become involved. In the meantime, it might seem appropriate to further consider the relationship between 'capillary filling' and the equilibrium which must be maintained between the intra-vascular volume, 'Vs', and the volume of the extra-vascular fluid, 'Vx'. If exchange of fluid between these two compartments only occurs in the capillary region ( i.e., between the spatial limits provided by the arterioles and the venules) , it must be closely related to the volume and energy level of the blood present in this area. As previously pointed out, this energy is for the most part kinetic energy of flow, represented as momentum, 'D.Vs.v', while the energy required to overcome resistance, and also represented as momentum, is 'R.Vs', or vascular filling. At the same time, fluid will be leaving or entering the capillary circulation depending on the concentration and osmotic pressure of the plasma proteins, and on the volume and energy level of the extra-vascular fluid. The factors influencing capillary filling then become 'momentum/osmotic pressure of plasma', and 'vascular filling / extra-vascular velocity times oxygen concentration'. Expressed symbolically this becomes

$$D.Q.lPR . R.Vs / (OPP . vx . [O_2])$$

For given permeability of the capillary membrane, (indicated by  $[O_2]$ ) the osmotic pressure of plasma protein is proportional to l.PR, while 'vx' is proportional to 'Vs /  $[O_2]$ '.

The above expression would then be equivalent to 'Q.OPP/vx', or 'Q.R'. Because the vascular filling, 'R.Vs', is related to the osmotic pressure of the plasma and oxygen concentration, any variation in R.Vs / OPP will be limited or negligible under most

circumstances, so that the stroke volume, 'Q', and ventricular filling 'Q.R' become the main parameters determining capillary filling, and the exchange of fluid between 'Vs' and 'Vx', while the circulatory ratio (Q/Vs, v/IPR, [CO<sub>2</sub>].[O<sub>2</sub>], etc) remains unchanged. In general terms, 'filling' in different regions such as ventricular filling, capillary filling, and the increase in extra-vascular volume, cellular volume, and venous volume with each ventricular beat, will all be functions of 'Q.R', which represents 'ventricular filling', but the significance of this 'filling' will alter as 'Q' varies with respect to 'R', because the actual volume of fluid transferred in each case is directly related to stroke volume, and will vary directly with changes in the value of 'Q', and inversely with changes in 'R'.

'Capillary filling' is seen to be a critical factor regulating the transfer of fluid and energy between the intra-vascular and extra-vascular fluid compartments. It can be varied by alteration of most of the parameters involved in energy production and transfer within the fluid compartments of the body, and which may in turn affect stroke volume, ventricular filling, and the osmotic pressure exerted by the plasma proteins. For this reason it can be shown to be related to :-

1. Energy provided by the ventricle per beat / OPP .
2. Energy required to be present in the circulation per beat times Q / Vs (relative amount of circulating volume present in the venous system, and proportional to R.Vs.OPP) .
3. Stroke volume / systemic blood volume times vascular filling, i.e., APs, modified by plasma osmotic pressure; or ' $[CO_2] \cdot l^3 \cdot \eta / OPP$ ' ; or ' $Q^2 \cdot l'$ ' , if 'OPP' is constant; or ' $Q^2$ ' if 'l' is constant; ' $R^2$ ' if Q is constant , i.e., to v if Q is constant . Capillary filling can then be maintained by alteration in the values of 'Q', 'R', 'v' and 'l.PR', or by alteration of 'Vs', and/or 'OPP' for given values of '[CO<sub>2</sub>]' and 'l.PR', while if '[CO<sub>2</sub>]' and '[O<sub>2</sub>]' remain constant, filling depends almost entirely on 'l' cubed. (The significance of 'l' cubed as an indication of [lactate] is addressed in later text). In summary the above relationships mean that capillary filling and subsequent exchanges with the extra-vascular compartments depends on :-

1. Flow allowed from the arterioles , i.e., [O<sub>2</sub>], 'R' .
2. Flow allowed in the venous capillaries and venules, i.e., [CO<sub>2</sub>] , 'Q'.
3. Energy provided by ventricular contraction in order to maintain kinetic energy by altering 'v', i.e., 'l' and 'PR'.
4. The residual momentum required in the circulation at diastole, i.e., 'R.Vs' and circulatory volume 'Vs' .
5. Osmotic pressure of the plasma proteins required to maintain the ratio of Vx/Vs , i.e., the protein concentration or  $\propto$  'D'.

The function of the intra-vascular circulation is to maintain capillary filling at an adequate level for maintenance of 'Vx' and 'Vc', and the store of momentum (R.Vs) which balances energy exchange with the cells, so that the exchange is able to increase with increase in

stroke volume, 'Q', but to decrease with increase in 'R', with appropriate adjustments of 'Vs.R' and 'Q.R', so that the circulatory ratio Q/Vs is maintained. The appropriate level for adequate activity (set by the oxidative activity of the respiratory enzymes) determines the circulatory ratio (Q/Vs etc) which is then reflected in the other circulatory parameters. In practical terms, 'capillary filling' is affected by the concentration of lactate (see later text) times l.vx.[CO<sub>2</sub>]; or [lactate].l.PR./[O<sub>2</sub>]; by stroke volume times 'R.Vs/vx.[O<sub>2</sub>]; or by ventricular filling. The 'store' of energy which remains in the extra-vascular circulation from beat to beat is important for the distribution of energy between effector cells and the venous return, and needs to be distinguished from the kinetic energy contributed from the intra-vascular circulation at systole, and returned to the venous circulation before the next beat, as well as the persisting flow energy throughout the cardiac cycle. This implies three amounts of energy which may be quantified; first the momentum in the tissue fluid at diastole, or 'l.PR . vx', representing 'flywheel type' energy and proportional to 'PR<sup>2</sup>'; secondly energy contributed by each ventricular contraction and having the momentum equivalent proportional to 'Q.R'; and thirdly energy which balances the energy contained within the cells at diastole, and ensures that equivalent energy remains in the cells following depolarisation, e.g., following muscle contraction. The amount of the latter is the 'stored energy', and it remains equivalent to the cell energy store at diastole, or 'R/vx' inside the cell balanced by 'R/Vs' outside the cell while passive permeability equivalent to '[O<sub>2</sub>]' preserves a similar factor for energy store between the two. Energy in the extra-vascular circulation at systole is equivalent to 'v.Q.' from the ventricle times 'Q.R.vx' from cells, which is equivalent to the kinetic energy given to stroke volume per beat, and the total energy  $\propto Q .v^2 .Vs$ .

An amount of energy equivalent to 'R/Vs' represents 'stored energy' in the extra-vascular fluid, which persists from one beat to the next to preserve the energy balance and exchange with the cells, and this represents the energy equivalent of the lactate concentration, or [lactate]. This equivalent amount of energy must always be available to preserve an adequate circulation. The energy equivalent for [lactate] in the polarised cell is 'R/vx', or 'R.L/PR', which may be reduced to 'l. [O<sub>2</sub>]<sup>2</sup>'. While the cell remains polarised, passive permeability maintains an energy difference across the membrane proportional to the oxygen concentration, and the energy equivalent of lactate concentration in the tissue fluid is proportional to 'R/Vs'.

Some further comment upon the exchange of fluid and energy between the capillaries and the extra-vascular fluid, together with its relationship with ventricular activity may now be made. Exchange of fluid and energy is only possible in the capillary network, and the energy per beat provided by the ventricle and available for this purpose is proportional to Q.R.LPR. The other portions of the vascular system, the arteries and veins, simply serve as conduits between the heart and the capillary bed, though these vessels are modified in certain ways to assist in the exchange of mechanical forces which are essential for fluid

exchange to occur with extra-vascular areas. For example, the arteries with their muscular and elastic walls, allow transmission of potential energy to the periphery, where it is converted to kinetic energy of flow by forcing blood through much smaller vessels, the arterioles.

This allows adjustment of the linear velocity of flow, and the transmission of momentum to the much larger volume of fluid in the extra-vascular tissue spaces. The thinner walled veins have a much more flexible volume than the arteries, and this property allows more adjustable volume/pressure/linear velocity of flow relationships within the blood returning to the heart. These adjustments have particular significance for ventricular filling, and the relationship between volume flow and energy content of blood leaving the heart, which have already been considered in earlier sections.

Transmission of momentum is associated with movement of fluid from one area, the blood, to the extra-vascular fluid and back again, and this movement requires adjustment of local forces and barriers which are necessary elements regulating the amounts of fluid and energy transferred, and the freedom with which it is able to move. Before any such movement can occur, sufficient blood with the correct amount of energy must be supplied to the capillary network, resulting in an adequate level of capillary 'filling', i.e., a volume of blood containing the correct level of energy, presented in a suitable mix of potential (pressure) and kinetic (linear movement) energy. It is these adjustments which need to be understood for proper assessment of the extra-vascular circulation.

The first essential in capillary 'filling' is the vis-a-tergo, the energy supplied by ventricular contraction, which forces fluid into the capillary system with energy content adjusted by passage through the arterioles. The total energy available in the circulation for this purpose is proportional to the product of ventricular filling and the force of ventricular contraction, and this provides the conditions, which in association with the osmotic pressure produced by the concentration of plasma proteins, allows a balance to be achieved between the intra-vascular and extra-vascular fluid volumes by exchange in the capillary bed, in the manner suggested by Starling's original investigations (Starling, 1895-9). The filling of the capillary bed must also depend on the freedom with which fluid is able to move in each direction across the capillary wall, ultimately regulated by the balance between the osmotic, intra-vascular, and extra-vascular fluid pressures, which can all be included in a resultant pressure difference and expressed by the symbol 'OPP'. The balance of volumes,  $V_x/V_s$ , will then depend on the energy balance,  $Q.R.IPR/V_x.OPP$ , or proportional to  $APs/OPP.Q$ , or  $R/Q$ .

While this balance may be adequate for description of the 'average mean' conditions which prevail, it is constantly being altered by injection of further energy and volume changes associated with the cardiac cycle, so that the volume increases by 'Q' during systole, and is reduced again by 'Q' by the end of diastole, when this volume is accommodated in the ventricle once more. Movement of fluid from the intra-vascular to the extra-vascular

compartment , requires energy equivalent to Q.OPP, and may be represented as follows;

Energy present in the circulation times  $Q/(V_x.[O_2])$  is proportional to Q.OPP, or  $Q.R.I.PR.Q/V_x.[O_2]$  is proportional to Q.OPP because  $V_x$  is proportional to  $Q.R.I.PR/OPP.[O_2]$  . Now 'OPP' is proportional to the residual momentum or resistance required in both the intra- and extra-vascular systems , because  $v_x.[O_2]/v$  is proportional to  $V_s/V_x$  , and the momentum in each system is proportional to that in the other. Increased capillary filling at systole is therefore proportional to Q.OPP, or  $Q.R.V_s/[O_2]$ , or  $Q.R.v_x$  , which represent the product of 'ventricular filling', 'Q.R', with circulatory volume/ $[O_2]$ , or alternatively , the product of 'QR' with the average mean linear velocity of flow of fluid present in the extra-vascular space.

The kinetic energy available to transfer fluid back into the vascular system from the extra-vascular space is equivalent to 'Q.R.vx', while the kinetic energy supplied to fluid passing from the intra- to extra-vascular compartments is proportional to 'Q.R.v' which must be somewhat greater in amount. This estimate is the mean value based on the average mean linear velocity of blood in the systemic circulation throughout the cardiac cycle, but the value of velocity at any instant will be variable about this mean, so that the addition of momentum to the extra-vascular fluid is greater in the early part of the cardiac cycle, and somewhat less in the latter part. The actual movement of fluid and energy then depends on the ratio of intra-vascular/ extra-vascular velocity, or  $v/v_x$ , where the value of 'v' depends on a greater linear velocity in the blood vessels during systole, while the value of 'vx' might largely result from a relatively greater linear velocity of extra-vascular fluid during diastole. For example, if the momentum in one compartment is proportional to that in the other, this can be represented as  $V_s.v$  is proportional to  $V_x.v_x.[O_2]$  , so that  $v/v_x$  is proportional to  $V_x.[O_2]/V_s$  . Conservation of momentum between the two systems would then require that the greatest volume of fluid has the least linear velocity, and the relationships between 'v', 'R', and 'vx' which result, are crucial for the transfer of fluid in each direction. In order to maintain the values of 'Q' and 'Vs' at an adequate minimal level to sustain the circulation, the linear velocity of fluid in the circulation must increase as 'R squared', while the osmotic pressure limits the value of the linear velocity of extra-vascular fluid as 'R' is increased, so that  $D.v$  is proportional to R squared, and  $R.v_x$  is proportional to OPP. If for some reason the value of 'R' is increased, an increase in 'v' becomes necessary in order to preserve the values of 'Q' and 'Vs' at somewhere close to adequate levels, while at the same time the value of 'vx' will be reduced for a given protein osmotic pressure.

Maintenance of adequate fluid exchange then depends on an increase in the value of 'v', and therefore of the ratio  $V_x/V_s$ . If (because of the increase in 'R') 'v' is increased as 'R squared', 'Vx' also increases as 'R squared', and maintenance of 'Q.R.vx' requires an increase in 'Vx' to keep 'Vx.vx' at its previous level, which will now be proportional to 'R

squared'.vx. This means that the ratio of  $V_x/V_s$  becomes proportional to  $\sqrt{R \cdot V_s}$ , and requires a considerable increase in momentum in each system, while  $\sqrt{v/R}$  still determines the ratio of extra-vascular to intra-cellular volumes, and  $\sqrt{v}$  must increase as  $\sqrt{R}$  squared' to maintain the balance with the cells. Because  $\sqrt{v/R}$  represents momentum in the extra-vascular fluid, this momentum must increase by a more rapid increase in  $\sqrt{v}$  compared with  $\sqrt{R}$ , and the increase will only be adequate to preserve the circulation if  $D \cdot v$  is proportional to  $\sqrt{R}$  squared'. Transfer of fluid between compartments must then depend on this ratio of  $\sqrt{v/R^2}$ , proportional to  $PPs/APs^2$  for a given value of  $\sqrt{l \cdot PR}$ , in order to preserve fluid exchange and ventricular filling, albeit with a diminished value of  $\sqrt{Q}$  relative to the value of  $\sqrt{R}$ .

Exchange of fluid with the capillaries is at the same time subject to the tissue oxygen concentration in the region, which is directly related to capillary permeability. As oxygen concentration diminishes along the length of the capillary, its permeability increases, and the relative value of the osmotic pressure exerted by the plasma proteins diminishes. As the oxygen concentration diminishes, the value of  $\sqrt{R}$  will also be diminished, but this is offset by a relative change in 'apparent viscosity' of the blood, or  $\sqrt{\eta}$ , which increases as the oxygen tension falls. If  $\sqrt{R}$  is proportional to  $l \cdot \eta \cdot [O_2]$ , the fall in blood  $[O_2]$  leads to an increase in  $\sqrt{\eta}$ , and vice versa, and the overall value of  $\sqrt{R}$  is largely maintained as the oxygen tension in venous blood approaches that of the tissues more closely with the rapid change in oxygen partial pressure of blood inside the vessels. Because it is the viscosity of the blood which is variable, change in apparent viscosity, or  $\sqrt{\eta}$ , might be expected to have its main significance within the vascular system alone, the apparent viscosity of other body fluids being relatively unaffected. It should be pointed out that the values of  $\sqrt{R}$ ,  $\sqrt{v}$ ,  $\sqrt{Q}$ , etc. which are used to provide equivalent values whether inside or outside the vascular system, are those which are determined by events and forces within the vascular system in the first instance, and which have secondary effects extending outside its confines, by reason of the equilibria which exist across tissue membranes; and any variation in, for example,  $\sqrt{R}$ , within the blood vessels, applies to its value elsewhere. This is despite the relative stability of viscosity which may be present in other body fluids.

The previous discussion introduces an interesting comparison between the two parts of the vascular circulation which conduct blood to and from the capillary bed and the heart. The function of the arterial system is conventional enough. The vessels have elastic and muscular walls, which assist in the storage and conversion of potential to kinetic energy, and it is in this form that it is presented to the capillaries. But beyond the capillaries, the residual energy is already in the form of kinetic energy. It is conveyed in this form in the veins, and it is still largely as kinetic energy that it is presented to the cardiac chambers. While resistance to flow in the arteries (or the momentum equivalent which has to be overcome for flow to occur, represented as  $\sqrt{R}$ ) is then appropriately varied by alteration in the diameter of the vessels, reducing potential energy, and converting it to kinetic energy in the arterioles, such measures to regulate linear velocity of flow, is entirely inappropriate

in the veins. There, the kinetic energy presented to the venous blood, is modified by altering the internal resistance or 'viscosity' of the blood. This is still effected by changing the oxygen concentration of the blood, which becomes more viscous as the oxygen level falls, with reduction of oxyhaemoglobin to reduced haemoglobin (in other words by alteration of the ratio  $\text{HbO}_2/\text{Hb}$ ) which increases the 'apparent viscosity', or ' $\eta$ ', and so maintains 'R' proportional to  $l\eta[\text{O}_2]$ , because ' $\eta$ ' varies inversely as  $[\text{O}_2]$ , while the venous diameter is perhaps less sensitive to oxygen concentration, and responds more readily to carbon dioxide concentration, though in the opposite direction. The partial pressure of oxygen in the tissues then influences the value of 'R' on the arterial side by variation of the cross sectional area of the blood vessels, but on the venous side by altering the internal resistance, or viscosity of the venous blood, which may also vary directly with changes in linear velocity of flow (Pappenheimer & Maes, 1942). The result is that 'R' and 'Q.R' can be maintained in venous blood independently of any alteration in the cross sectional area of the vascular bed, so that linear velocity may be maintained in vessels with quite slack walls, with little lateral pressure applied to them, and this linear velocity of flow is in the main responsible for the amount of venous return and ventricular 'filling'. Regulation of the linear velocity of flow becomes a function of the force of ventricular contraction (I.PR) and/or the free energy present in the effector cells, as set out in chapter 4. Vasoconstriction can still occur in the veins, where its function is to adjust vascular volume, and as a result, linear velocity of flow / lateral pressure on the venous walls, for regulation of stroke volume / pulse rate or the volume / velocity relationship of the cardiac output.

Returning once more to the volume exchange in the capillaries, it would appear that this depends directly on the size of the stroke volume. The energy exchange is proportional to Q.OPP, while the energy remaining in the vascular system is proportional to  $V_s$ .OPP, and the fluid exchange is directly related to the circulatory ratio  $Q/V_s$ , which is equivalent to the product of the gas concentrations or  $[\text{O}_2].[\text{CO}_2]$ . The exchange between the cells and extra-vascular fluid is proportional to  $v/R$ . But  $v/R$  is proportional to momentum in the extra-vascular space, ' $V_x.v_x$ ', and for stroke volume and circulating volume to be maintained,  $D.v$  must vary as 'R squared', which is proportional to ' $V_x$ '. The residual momentum in the extra-vascular space is  $V_x.R$ , and this 'stored' residual momentum is proportional to ' $R^3$ '. Within the cells, the retained or 'residual momentum' is ' $V_c.R$ ', and as ' $V_c$ ' is proportional to 'R', 'stored momentum' is proportional to ' $R^2$ '. Within the vascular system, residual momentum is 'vascular filling' or  $R.V_s$ . Increase in the value of 'R' will then increase vascular filling unless ' $V_s$ ' is reduced, so that maintenance of ' $V_s$ ' requires an increase in the value of ' $R.V_s$ ' or ' $l^2 \eta$ ', and this will require that 'stored' or residual momentum in the extra-vascular fluid increases as ' $R^3$ ' (or ' $v.R$ ' where ' $D.v$ ' is proportional to ' $R^2$ ') and momentum 'stored' in the cells increases as ' $R^2$ '. Both ' $V_s$ ' and

'Q' are likely to be reduced in value, but can be maintained at a relatively adequate level if pulse pressure varies as the square of systolic pressure, and vascular filling is kept relatively constant, as previously set out.

Adequate fluid exchange in the periphery then depends upon adequate stroke volume, and adequate vascular filling (set by the value of OPP) . Readjustment of the elements of capillary filling, i.e.,  $Q.R.Vs/[O_2]$  ,  $Q.R.vx$  , and  $Q.OPP$  , which are all proportional to each other, and represent energy equivalents, can also be represented as ' $Q^2 Vs$ ' (where ' $Q^2 Vs$ ' is proportional to ' $vVs$ ' or circulatory momentum), while the forces or momentum transferring energy and fluid, ' $Q.v$ ', and  $Q.l.PR$ , are also important and relate the exchange to linear velocity of flow and the force of ventricular contraction. A limiting factor in the transfer is the osmotic pressure of the plasma proteins, which is proportional to ' $vx.R$ ' and ' $Vs.R/[O_2]$ '.

When the stroke volume is enlarged compared with ' $R$ ', and vascular filling, (and also with linear velocity of flow if ' $v$ ' is proportional to ' $R$  squared'), it leads to an increase in momentum affecting both the intra-vascular and extra-vascular compartments, where the momentum is proportional to ' $Q.l.PR$ ' , and ' $v.Vs$ '. In the extra-vascular compartment increase in momentum, and 'energy storage', can occur through increase in volume, ' $Vx$ ', or by increase in linear velocity of the extra-vascular fluid, ' $vx$ ', and reflects reciprocal changes in intra-vascular volume and velocity. Enhanced linear velocity of blood flow, results in a larger volume of extra-vascular fluid, ' $Vx$ ', which is proportional to  $Q.R.l.PR/(OPP.[O_2])$ , while increase in stroke volume (proportional to ' $Vs.l$ '), leads to an increase in linear velocity of flow in the extra-vascular fluid, or ' $vx$ '. It follows from this , and the relationship ' $vx.R$  is proportional to  $OPP$ ' , that increased ' $vx$ ' also involves a relative reduction in the value of ' $R$ ', together with the amount of energy 'stored' in the cells, while ventricular filling then depends more upon increased stroke volume, and less upon the momentum equivalent which has to be provided to overcome resistance in the circulation. The overall 'storage of energy' in the extra-vascular compartment is then reduced at the same time that venous return is increased.

Any increase in the value of ' $R$ ' leads to an enlarged 'energy storage' in the extra-vascular compartment proportional to ' $R^3$ ', and in the intra-cellular compartment proportional to ' $R^2$ ', with reduction of stroke volume, and venous return for the same 'ventricular filling'. Enlargement of intra-cellular volume and energy content then becomes a significant feature. Greater values for ' $v$ ' or ' $l.PR$ ' result in greater extra-vascular volume, ' $Vx$ ', rather than linear velocity of flow, ' $vx$ ', and also in greater intra-cellular volume to maintain the ratio ' $Vc/Vx$ '; but if ' $D.v$ ' increases more rapidly than ' $R^2$ ', an increase in stroke volume is then part of the adjustment, with ' $Vs$ ' increasing more rapidly than ' $Vc$ ', because of the

relative fall in the value of 'R'. 'Energy storage' associated with the greater values of 'v' and 'l.P.R' is then mainly concentrated in the extra-vascular compartment, and later returned to the intra-vascular compartment as increased linear velocity of flow, and/or stroke volume, unless there is an associated rise in the value of 'R' (and of R/IPR) which transfers energy instead into the cells, rather than into the venous return. The value of 'R' is critical for the distribution of fluid and energy between the three compartments of body fluid, and is itself regulated by the oxygen partial pressure maintained in the tissue fluids. Stroke volume, on the other hand, largely depends on the partial pressure of carbon dioxide, and increase in this partial pressure, directs fluid and 'energy storage' away from the cells, and towards the intra-vascular circulation, the venous volume, and the venous return.

The nature of 'R', or the momentum which must be provided to unit volume of blood in the systemic circulation, in order to overcome 'resistance' to flow along its vessels.

In the arterial system, the determination of the necessary momentum is fairly simple. If 'R' is related to 'l.η/a', it is the length and cross sectional area of the vascular bed which are the important features. The cross sectional area of the vessels is reciprocally related to oxygen concentration, and 'R' is proportional to 'lη[O<sub>2</sub>]'. While the dimensions 'l' and 'a' relate it to the physical dimensions of the vascular bed, 'R' is also proportional to 'η', or 'apparent viscosity', i.e., to the internal resistance presented by the blood itself. In the arterial system, where the linear velocity of flow is relatively large, and the oxygenation of arterial blood is relatively constant, 'η' also remains relatively constant, and has little influence on the relationship involving 'R', 'l', '[O<sub>2</sub>]', and 'η'.

The arterial system is concerned with the provision of blood to the capillaries with a certain momentum and linear velocity, and this is controlled by adjusting the arterial pressure, and the diameter of the vessels through which the blood passes, so that the potential energy of pressure is largely converted into linear velocity of flow, that is the form of energy involved in energy and fluid exchange between the fluid compartments of the body. Energy in the form of momentum is transferred to the extra-vascular and intra-cellular compartments, and then released back again to the venous system to provide cardiac and ventricular filling, 'Q.R'. Some energy is lost in this transfer, which also requires energy to be 'stored' and then released again into the venous system in order to maintain venous return. 'Storage' of energy occurs in the extra-vascular compartment by increase in volume and/or linear velocity, but mainly by volume increase. When energy returns to the vascular system, the momentum contributed depends on the reduction of extra-vascular volume. Energy 'storage' in the cells occurs through variation in the values of 'v' and 'R', as already outlined.

Once energy returns to the venous system, the nature of the variables determining its value has now changed from those of most importance in the arterial system. The value of 'R' now reflects change in the 'internal resistance' or 'apparent viscosity' of the venous blood, while the lateral pressure, and physical dimensions of the blood vessels are of less

consequence. Provided the linear velocity of flow is sufficient, lateral pressure remains negligible, the venous walls remain slack, and the vessels appear 'underfilled' compared with their potential volume. The value of 'R' now depends on the values of 'l' and ' $\eta$ ', rather than on 'a' and 'l', but is still related to tissue oxygen partial pressure, because the 'apparent viscosity' varies with the relative amounts of HHb and HbO<sub>2</sub> present in venous blood, and therefore with the degree of oxygen saturation of the blood; and on oxygen concentration in the tissues. The shape of the oxygen dissociation curve for haemoglobin makes it unlikely that the inverse relationship of ' $\eta$ ' and '[O<sub>2</sub>]' is linear, and in any case ' $\eta$ ' also varies with change in linear velocity, as recorded by a number of observers investigating the rheology of blood (e.g. Pappenheimer and Maes, 1942). Nevertheless, the effect of oxygen concentration on resistance to blood flow which follows from changes in vascular diameter, and that which follows from alteration in Haemoglobin saturation are in opposite directions and oppose each other. This makes the final effect of [O<sub>2</sub>] on the overall average mean value of 'R' rather complex, and there are consequences which flow from this complexity.

1. Because the circulatory ratio [O<sub>2</sub>].[CO<sub>2</sub>], needs to be largely maintained between limits allowing an adequate circulation, any fall in oxygen concentration needs to be compensated by a rise in carbon dioxide level, which would therefore appear to have a similar result for blood viscosity, which will increase as carbon dioxide concentration rises.
2. Because oxygen concentration has different effects on the value of 'R' on each side of the capillary bed, a fall in oxygen level increases the inflow of blood from the arterioles by reduction in vascular tone, while increased viscosity of blood resists the outflow, and therefore increases capillary 'filling'. This increase in filling leads to increase in vascular cross section as well as length, with increased lateral pressure as the linear velocity is reduced, and 'R' increases, but the rise depends on alteration of linear velocity rather than alteration of cross sectional area of the vascular bed.

The value of 'R' then depends on vasoconstriction on the arterial side, but on altered 'apparent viscosity' on the venous side of the capillary bed, and the relationship between the two depends on the ultimate value of oxygen partial pressure present in the tissues. As oxygen concentration increases, vasoconstriction becomes more intense on the arterial side, while vascular volume and diameter decreases on the venous side, accompanying the decrease in viscosity and increased linear velocity of the venous blood, and the overall reduction in cross sectional area of the circulation. Blood volume is still proportional to 1/[O<sub>2</sub>], while 'R' is proportional to 'l.[O<sub>2</sub>]. $\eta$ ' as previously claimed, though this may be overly simplistic, and the relationships only approximate (because of non-Newtonian flow relating 'v' and ' $\eta$ ', and the 'S' shape of the oxygen dissociation curve for haemoglobin). When tissue oxygen concentration is diminished, vasodilatation occurs on the arterial side, while 'apparent viscosity' is increased in venous blood, but the result is an increased vascular diameter in each set of vessels. Variation of venous volume and diameter has significance for regulating stroke volume, while variation of linear velocity of flow, has

a major role in adjusting the force of ventricular contraction and pulse rate, as already outlined in chapter 5. These adjustments ultimately depend upon changes in oxygen concentration and 'apparent viscosity' of venous blood. Capillary 'filling' and the associated fluid exchange with the extra-vascular compartment then become largely dependent on the ratio 'Q/Vs', or the product  $[CO_2].[O_2]$ , the circulatory ratio.

*Outline of the dynamics of the extra-vascular circulation in everyday terms.*

A main function of the cardio-vascular system is to supply blood to the capillaries with given values for linear velocity of flow, stroke volume, and rate of perfusion against a resistance to flow having an energy equivalent per ml. equivalent to 'R', or momentum per ml. of blood which must be present before any flow can occur in the system. Energy exchange between the intra- and extra-vascular compartments is regulated by the linear velocity of blood presented to the capillaries, and the osmotic pressure exerted by the plasma proteins, so that the ratio of linear velocity of flow and the osmotic pressure of plasma proteins together determine the distribution of fluid between the two compartments for any given value of momentum provided by ventricular contraction. Filling of the capillary bed is proportional to 'Q.R.Vs', which is also equivalent to ' $l^3 \eta [CO_2]$ ', or ' $l^4 [CO_2]/[O_2]$ ' (i.e., ' $l^3 PR$ ', the peak arterial pressure).

When the average mean linear velocity, 'v', of the blood increases, momentum in the extra-vascular fluid also increases, represented by an increase in the volume of the compartment, 'Vx'. If the stroke volume should be increased, the momentum in the extra-vascular fluid is again increased, but this is represented by an increase in linear velocity of fluid in this compartment, or 'vx', so that 'vx' is proportional to 'Vs' (the intra-vascular volume) /  $[O_2]$ .

Should the residual momentum required in the system to overcome resistance per ml. of blood, represented as 'R', be increased, stroke volume is reciprocally affected, to preserve vascular filling, 'R.Vs', and ventricular filling, 'Q.R'. While the relative volumes of the intra-vascular, and intra-cellular compartments may vary; with a relative increase in 'Q' increasing intra-vascular volume, and a relative increase in 'R' increasing intra-cellular volume, the product 'R.vx' is limited by the value of 'OPP', which also limits 'R.Vs' /  $[O_2]$ .

The extra energy provided to the extra-vascular fluid as the linear velocity of the blood increases, results in increased momentum in this compartment, represented by an increased volume, 'Vx', but energy provided by enlargement of the stroke volume, 'Q', also appears as increased linear velocity of flow of the extra-vascular fluid, or 'vx', and the total momentum provided to the extra-vascular fluid per beat is proportional to the product 'v.Q'. Of this momentum, the relative distribution between the tissue cells, and the blood, is

regulated by the ratio  $Q/R$ , so that as stroke volume increases, so does the relative energy level within the blood vessels, while increase in  $R$ , increases the momentum used to increase cellular volume, which is proportional to  $R$ . Any increase in stroke volume, while it produces increasing momentum in the extra-vascular fluid, also results in a greater volume of fluid passing back into the intra-vascular compartment, with augmentation of the venous return, with much smaller energy expenditure and lowered values of  $R$ , and  $l.PR$ , or systolic blood pressure. On the other hand, an increase in  $R$  (or necessary momentum per ml. of blood, to overcome resistance to blood flow) also restricts stroke volume, because of the reciprocal relationship set by the value of plasma osmotic pressure, and more energy is then diverted towards increasing intra-cellular volume, and the amount of energy retained or 'stored' in the cells.

At the same time, relatively less energy is then available to maintain linear velocity in the extra-vascular compartment, or  $v_x$ , and as a result, the volume of fluid returned to the intra-vascular compartment to maintain the values of  $Q$ , and  $V_s$ , will be reduced unless there is an increase in the total momentum provided by increasing  $v$  (and so the extra-vascular volume) in addition to the increase in  $R$ , the intra-cellular volume. This requires an increase in  $R.l.PR$ , or systolic blood pressure, from increased energy output by the left ventricle, in order to maintain an adequate circulation and energy exchange with the cells and the extra-vascular circulation. While the momentum transferred to the extra-vascular compartment per beat is proportional to  $Q.v$ , the momentum 'equivalent' which is needed before any movement occurs is proportional to  $Q.R$ , or ventricular filling, and is also proportional to the cellular energy exchange required, and to the momentum transferred back into the venous system again to achieve ventricular filling. The momentum required to be added to the extra-vascular compartment to produce this cellular exchange (proportional to  $Q.R$ ) is then proportional to  $Q.v$ , and the resultant momentum required in the extra-vascular compartment is proportional to  $v/R$ . However when  $R$  increases,  $v$  must increase as  $R$  squared in order to maintain this exchange. Because  $v/R$  is proportional to  $PPs/APs$ , for a constant value of  $l.PR$ , adequate exchange between the cells and extra-cellular fluid can only occur when pulse pressure increases proportionally with  $APs$  squared, the square of the systolic arterial pressure in the systemic circulation. At the same time it requires a contribution of energy from cell metabolism equivalent to  $l.PR$ , the free energy present in the 'effector cell'.

While kinetic energy of flow is provided to the blood entering the capillaries by conversion of potential (or pressure) energy 'stored' in the arterial walls, by forcing the blood through arterioles having the required degree of constriction, the kinetic energy produced in this way, and represented by the linear velocity of flow,  $v$ , may be 'stored' in the extra-vascular fluid as increased volume in this compartment. Any increase in kinetic energy in this compartment occurring because of an increase in stroke volume, and/or linear velocity of extra-vascular fluid, is not 'stored' energy, but that part of the original kinetic energy provided which has not been 'stored', and as this proportion increases, the amount of 'stored' energy in the extra-vascular fluid as a proportion of the total kinetic energy present,

and represented by the fluid volume, ' $V_x$ ', is consequently reduced. Because ' $V_x$ ' is proportional to ' $v$ ', reduction in this volume, whether relative or absolute, requires similar reductions in the values of ' $v$ ', and also of ' $R$ ' (because of the relationship required between ' $v$ ' and ' $R$  squared' for adequate cellular exchange) with a fall in cellular volume, together with its implied 'stored energy'. The result is a lower requirement for the level of systolic arterial pressure, ' $R.I.PR$ ', as the stroke volume, ' $Q$ ', is increased, and these adjustments indicate not only a greater volume exchange between compartments, but this greater exchange will also involve considerably reduced energy requirement, and slower pulse rate, while ventricular filling will now depend more heavily on stroke volume, and less upon the momentum equivalent which needs to be overcome for each ml. of blood in the systemic circulation.

These adjustments and energy exchanges are greatly influenced by

1. The level of plasma protein which is maintained in the blood, and the osmotic pressure which it is able to maintain (depending among other things on liver metabolism, and its regulation by venous reflux from the right atrium).
2. The partial pressure of oxygen present in the tissues, which
  - a. varies the activity of the respiratory enzymes, and so the metabolism of cells, together with the permeability of both capillaries, and cell membranes.
  - b. varies the relative concentration of oxyhaemoglobin compared with that of reduced haemoglobin in the venous blood, and so alters the 'internal resistance' or 'apparent viscosity' of blood, as the relative proportions alter, depending on the shape of the oxygen dissociation curve for haemoglobin.

In the arteries, ' $R$ ' is largely determined by the tissue partial pressure of oxygen which regulates the diameter of the arterioles, but in the veins it is ' $\eta$ ', 'the apparent viscosity' of blood, which is of greatest importance in regulating ' $R$ ', slowing the linear velocity of flow, and resulting in increased lateral pressure on the vein walls, and increased venous diameter.

In the capillaries, linear velocity of flow is likely to be slowed as haemoglobin becomes more reduced, and this assists energy and fluid transfer to the extra-vascular compartment, but as the blood approaches the 'venous end' of the capillary, the slowed flow reduces the transfer of fluid and momentum which depends on linear velocity. As the osmotic pressure of the plasma proteins becomes greater when they become more concentrated, and permeability of the capillary wall also becomes greater with the fall in  $[O_2]$  along its length, the linear velocity of fluid entering the capillary (proportional to ' $v_x$ ') is maintained at the expense of ' $V_x$ ', the extra-vascular volume, for a given value of momentum, depending on the value of stroke volume. (It should perhaps be pointed out that ' $V_x$ ' is dependent on ' $v$ ', which is difficult to maintain with increasing viscosity of venous blood, when the oxygen concentration there is falling. In general ' $v$ ' is maintained by the value of ' $I.PR$ ', which suggests that pulse rate needs to be accelerated as oxygen concentration is

reduced in the tissues.)

The venous return then varies as a function of oxygen concentration, an increased value resulting in less 'viscosity', and greater linear velocity compared with pulse rate, and a smaller lateral pressure on the vein walls, while decreased oxygen concentration results in greater 'viscosity', slowed linear velocity of flow, and greater lateral pressure on the walls of the veins. As previously suggested in Chapter 4, this results in altered ventricular size and shape, ventricular filling, stroke volume, and pulse rate. Stroke volume depends on carbon dioxide concentration rather than that of oxygen, and also on the vascular length, 'l', or capillary filling (but see Chapter 12,13). Also altered is the anatomical profile of the right ventricular cavity, and the dynamics of flow in the pulmonary circulation, where the pulmonary diastolic pressure is varied rather than stroke volume.

In the pulmonary circulation, a major difference from the systemic circulation occurs because of the re-oxygenation of haemoglobin in the pulmonary capillaries, which reduces the 'viscosity' of blood to the same level as that present in systemic arterial blood. As a result, the value of 'R' decreases, while the linear velocity, 'v', is able to increase, and the altered flow pattern produces an effect on left ventricular filling, which in turn has its own influence on right ventricular filling, stroke volume, and energy production as recorded in Chapter 8. As the viscosity of pulmonary blood falls, linear velocity of the blood becomes greater, while the lateral pressure in the veins (i.e., 'Vpp') is also reduced, with the implications such a fall might have on maintenance of ventricular efficiency, and the level of diastolic pressure which has to be maintained in the systemic circulation. Central to the whole pattern of energy exchange, is the partial pressure of oxygen which is required for adequate oxygenation in the tissue cells, and which influences the relative values of  $[CO_2]$ ,  $[O_2]$ , and vascular length, which in turn have significance for capillary filling, 'Q', 'R', and 'v'.

Oxygenation of blood in the lungs, may become a vital factor in adjusting linear velocity of blood flow in the pulmonary circulation, in the return of blood to the left ventricle, and in improving its efficiency. The adaptations which are necessary in response to alterations in the levels of carbon dioxide, oxygen, and circulatory length, in order to preserve adequate function, implicate metabolic processes in the control of circulatory activity. In particular, there is the probable relationship which appears to exist between 'circulatory length', and maintenance and control of the level of plasma lactate, together with the consequences which follow alteration in lactate level and/or circulatory length.

In addition there are mechanisms which are involved in the 'storage' of energy in the 'effector cells' to balance that presented to these cells in the form of kinetic energy from the extra-vascular circulation; and the circumstances and metabolic activity which allows the return of 'stored energy' to the venous system as increased venous return, when cellular and metabolic activity is increased.

*Summary.*

*Internal environment is maintained by continuous exchange between the fluid compartments of the body. Exchange in the capillaries is regulated by plasma protein concentration, and the permeability of the capillary wall as well as the required motion in the blood vessels. The fluid exchanged has kinetic energy of flow which it contributes to the extra-vascular compartment to regulate exchange with the cells, while allowing the fluid to bypass the capillary network, and reduce the resistance to flow offered by the latter. There are restraints on the general mobility of fluid imposed by the structure of connective tissues.*

*The change from potential energy (pressure) to linear velocity (kinetic energy) is accomplished in the aorta and arteries, and regulated by the arterioles. The momentum the fluid has depends on its volume and linear velocity. The momentum in each compartment is related to that in the other, but with a different volume and velocity component in each. Volume of the extra-vascular compartment depends on 'v' within the vessels, and the volume of blood is related to 'vx' in the tissue fluid, and oxygen concentration in the tissue cells. When the linear velocity of blood in the capillaries slows, momentum returns to it from outside the vessels, and gives increased momentum to the blood of 'venous return', again under the influence of the osmotic pressure of plasma protein.*

*The metabolism of the tissue cells is in large degree dependent on the turn over of fluid in its environment, where the resistance to flow is less than in the capillaries. There are limits to fluid movement, and the fluid volume acts as a repository for flow energy, after the manner of a flywheel. Fluid enters the space in a pulsatile fashion, but leaves in a 'linear' fashion. The energy 'store' is sustained by the active metabolism of the tissue cells, complementing cardiac activity. The linear velocity of the circulating blood becomes the determining factor for tissue fluid volume and momentum which is proportional to 'v/R' or the ratio of pulse pressure/ systolic pressure, which indicates the amount of momentum, while the volume is related to pulse pressure/ pulse rate. Greater momentum and volume in the extra-vascular fluid (proportional to l.PR) provides greater momentum and linear velocity to the venous return which is dependent on it, while the volume in the veins depends in turn on the linear velocity of fluid in the extra-vascular space. The volume ratios between 'Vs', 'Vx', and 'Vc', depend on changes in fluid dynamics, and vary as 'Q', 'l.PR', and 'R', (and the shape and volume of the ventricle at diastole). The internal resistance to blood flow, and the pulse rate, between them determine variations in fluid volumes, and this is also a function of the 'gas' concentrations. The utilisation of oxygen and its relationship with the oxygen concentration required, greatly influence the blood pressure required to maintain these levels, which together with permeability changes, affect the relative fluid volumes of body compartments. Time elements in contraction of ventricular muscle are emphasised in applications to the 'energy equation'.*

*Use of the finger plethysmograph, shows the fluctuations of extra-vascular fluid volume with the arterial pulse, and the passage of fluid in and out of the cells depending on 'Q', 'Vs', and 'R', and the linear velocity of flow in the fluid compartments. Vascular filling (Vs.R) has a considerable effect on the energy required in the circulation, and on 'Vx', and 'Vc'.*

