Chapter 8
The Microcirculation

Peter R. Hoskins

Learning outcomes

1. Describe the components of the microcirculation.
2. Describe the functions of the different components of the microcirculation.
3. Describe the variation of pressure and velocity with vessel type in the microcirculation.
4. Describe haemodynamic phenomena relevant to the microcirculation including plasma skimming; reduction and variability of viscosity and haemodynamics.
5. Discuss the origins of haemodynamic phenomena relevant to the microcirculation in terms of the behaviour of particles in small diameter tubes.
6. Describe the myogenic effect for arterioles (the Bayliss effect).
7. Discuss the control of blood pressure in the capillary by the Bayliss effect.
8. Describe the stress–strain behaviour of arterioles.
9. Describe pulse wave velocity in arterioles and capillaries.
10. Describe vasomotion and discuss how this may be a feature of the Bayliss effect.
11. Describe reasons for flow pulsatility in arterioles.
12. Describe the variation of wall shear stress for different vessels in the microcirculation.
13. Describe Starling's equation for diffusion of molecules across the capillary wall.
14. Describe transport of molecules across the capillary wall; diffusion, vesicular transport and bulk flow.
15. Describe 'flow autoregulation'.
16. Discuss the mechanisms for controlling flow; metabolic control, shear stress control, myogenic control.

P.R. Hoskins (✉)
Edinburgh University, Edinburgh, UK
e-mail: P.Hoskins@ed.ac.uk

P.R. Hoskins et al. (eds.), *Cardiovascular Biomechanics*,
DOI 10.1007/978-3-319-46407-7_8

8.1 Structure and Function of the Microcirculation

8.1.1 Structure

The microcirculation consists of those vessels of the cardiovascular system between the arteries and the veins; so the arterioles, the capillaries and the venules. Figure 8.1 shows a typical arrangement of vessels which are in the form of a network. The components of the microcirculatory network are described below. There is variation of values for both upper and lower lumen diameters in the literature; the values below are typical of those quoted in the literature:

- *Arterioles* (*diameter* 10–100 μm). These vessels are on the arterial side of the circulation. These branch several times and link the small muscular arteries to the capillaries. Arterioles contain three layers (intima, media adventitia), of which the media is proportionally the largest. The media is primarily comprised of vascular smooth muscle cells (typically, one or two layers in the larger arterioles with only a single spiralling layer in the smaller vessels leading to the capillaries). The residual tension in these cells, their tone, allows for alteration of arteriolar diameter and thus lumen size in response to changes in neural stimuli or in local chemistry. This plays a large part in control of capillary bed flow (see below) as well as the control of vascular resistance and systemic blood pressure.
- *Metarteriole* (*diameter* 10–20 μm). This term refers to an arteriole which is directly connected to a venule. This provides a vascular shunt which allows the capillary bed to be bypassed. In terms of structure, whilst metarterioles do not have continuous media, smooth muscle cells are present at the distal end of these

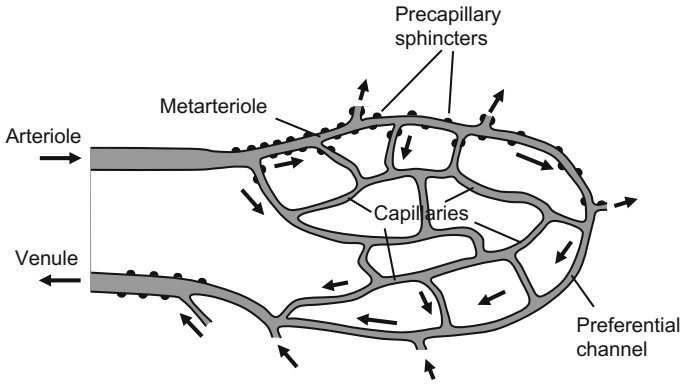

Fig. 8.1 Schematic of key microvessels and their organisation. On the arterial side is the arteriole and metarteriole. The metarteriole connect directly with the venule (on the venous side) forming a route (labelled as the 'preferential channel') which bypasses the capillary bed. Capillaries lie between the metarteriole and the venule; the capillary bed resembles a mesh rather than a bifurcating network. Precapillary sphincters are bands of smooth muscle which control flow in the capillary bed

vessels at the entrance to the capillary bed forming what are known as 'pre-capillary sphincters'. These can constrict to reduce flow into the specific capillary bed.

- *Precapillary sphincter*. The precapillary sphincter is a band of smooth muscle cells which controls flow into the capillary.
- *Preferential channel*. This is the channel between the metarteriole and the connecting venule. Constriction of the precapillary sphincters results in most flow travelling through the preferential channel rather than through the capillary bed.
- *Capillaries* (*diameter* 4–10 μm; *up to* 40 μm *in sinusoidal capillaries*). These are the smallest vessels in the cardiovascular system and, structurally are characterised as three types; continuous, fenestrated and sinusoidal. Capillaries consist of an endothelial layer and a basement membrane. Continuous capillaries have an uninterrupted endothelial lining and are the most common type of capillary. Fenestrated capillaries have pores in the endothelium which allow passage of certain molecules and are commonly found in endocrine glands, the gastrointestinal tract and the glomeruli of kidneys. Sinusoidal capillaries have large gaps in the membrane and an incomplete endothelial coverage which allows the flow of fluid and large molecules into the interstitial space. Sinusoidal cells are mostly found in the liver.
- *Venule* (10–200 μm). These vessels are on the venous side of the circulation, branching several times between the capillaries and the veins. Venules contain three layers (intima, media, adventitia), but these layers are much thinner than for arterioles and the medial layer is almost absent.

The above microcirculation architecture is commonly taught in textbooks. However, it has been pointed out that it is only the GI tract which has metarterioles in the sense of an arteriole with a discontinuous medial layer and precapillary sphincters. In other circulatory beds the term 'metarteriole' has come to refer to the smallest arterioles immediately before the capillaries.

It can be seen both from Fig. 8.1 and the discussion above that the capillary bed is not a conventional bifurcating network. There are bypasses in the form of 'preferential channels'; if precapillary sphincters are activated this can result in almost complete shut down of flow to the capillary bed. The capillary bed itself more resembles a mesh than a bifurcating network, so that there are multiple possible routes that a red cell can take through the bed.

8.1.2 Functions

The main functions of the microcirculation in terms of its components parts can be summarised as follows:

- *Resistance to flow*. Constriction of smooth muscle in the arterioles and the metarteriole enables control of local vascular resistance. This enables control of the pressure at the level of the capillaries and flow rate through the capillary bed.
- *Molecular exchange*. The exchange of fluid and of key molecules occurs through the walls of the capillaries. The main mechanism of exchange (diffusion) is pressure driven hence it is important to maintain hydrostatic pressure constant at the level of the capillary.
- *Flow bypass*. This refers to blood flow in vascular beds where the microcirculation contains a preferential channel controlled by precapillary sphincters. This allows particular capillary beds to be excluded from the microcirculation.
- *Capacitance*. The venules act as a reservoir of blood; some 22 % of the whole blood volume is contained in the venules.

8.2 Haemodynamics and Mechanics

8.2.1 Pressure and Velocity

In Chap. 2, basic concepts of cardiovascular biomechanics were introduced where it was noted that both blood pressure falls and blood velocity falls while travelling from the aorta to the capillaries. Rough estimates were provided in Table 2.1 of mean velocity based on a pure bifurcating model. Data on pressure and velocity in the microcirculation is shown in Fig. 8.2. This shows considerable decrease in pressure in the arteriolar part of the microcirculation, which is due to the high resistance to flow of arterioles. The pressure continues to fall through the capillary bed and the venules. Blood velocity is lowest in the capillaries with a value of around 2 mm s^{-1}. Table 8.1 shows values of mean velocity and other haemodynamic quantities in different vessels of the microcirculation.

8.2.2 Blood Flow

Blood is a suspension of particles, principally red cells. The human red cell dimensions of 7.5 by 2 μm, is tiny in comparison to the diameter of 1–30 mm of the larger arteries and veins. This means that in larger arteries and veins the blood can primarily be considered as a continuous fluid; or in other words, individual red cells can usually be ignored in considering haemodynamics. However in the microcirculation, the dimensions of the vessels are close to the dimensions of the red cell. This is especially true for capillaries where the typical diameter of 4–10 μm is comparable to the 7.5 μm diameter of the red cell. Red cells squeeze through capillaries in single file and are distorted in shape as they do so. Flow in the microcirculation is more complex than flow in larger vessels, and the effect of

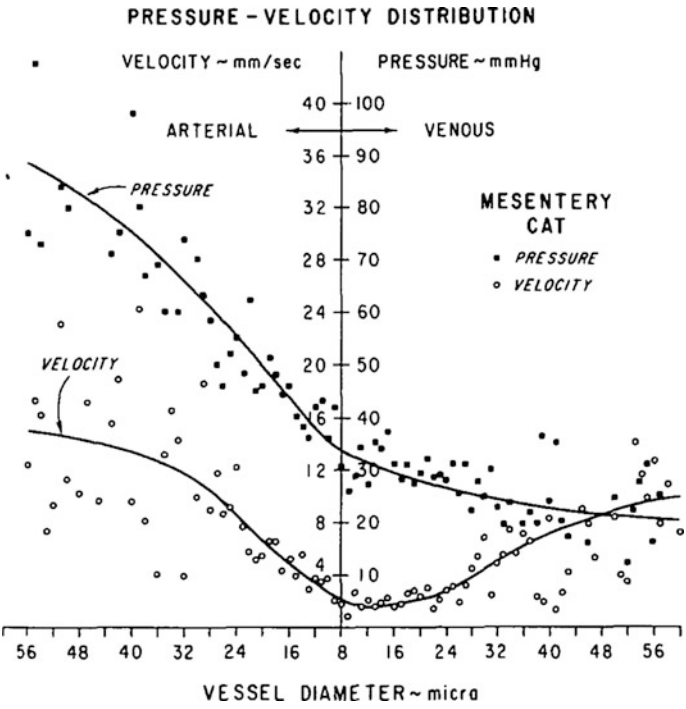

Fig. 8.2 Blood pressure and velocity in the microcirculation from arterioles to venules. From Zweifach BW, Lipowsky HH; Quantitative studies of microcirculatory structure and function. III. Microvascular hemodynamics of cat mesentery and rabbit omentum; Circulation Research; Vol. 41(3), pp. 380–390. Copyright American Heart Association (1977), reprinted with permission from Wolters Kluwer Health, Inc.

individual red cells must be considered. Chapter 3 describes a number of phenomena concerning flow of particles in tubes where the ratio of tube-diameter to particle-diameter is low and/or where shear rate is low. These phenomena are relevant to the microcirculation and are briefly summarised here.

- *Cell margination and depletion*. Particles flowing in a cylindrically shaped vessel will experience a number of forces. Some forces will push an individual particle away from the centre of the vessel and others will push the particle away from the vessel wall. This can lead to accumulation of particles in a ring between the vessel centre and the vessel wall. This is known as the Segre–Silberberg effect from the original paper (Segre and Silberberg 1962). Flow in blood is more complicated in that there are several different particle types; red cells are relatively deformable while platelets and white cells are relatively stiff. There is interaction between the particles in flow of whole blood. The red cells have a tendency to move away from the wall, leaving a layer near the wall depleted of red cells, while platelets and white cells are pushed by the red cells to the vessel wall (Aarts et al. 1988) as shown in Fig. 8.3.

Table 8.1 Haemodynamic quantities in the microcirculation

Vessel	Diameter (μm)	Mean velocity (mm s^{-1})	Reynolds number, Re	Womersley parameter, α	Pseudoshear rate (s^{-1})	Wall shear stress (Pa)	Effective viscosity (mPa s)	Haematocrit
Arterioles	60	12	0.2	0.8	200	6	2.8	0.29 ± 0.12
Arterioles	15	7	0.03	0.2	470	14	4.9	
Capillaries	5	0.2	0.0003	0.07	40	12	15	0.23 ± 0.14
Venules	18	0.2	0.001	0.2	10	3	4.2	0.31 ± 0.13
Venules	72	2.4	0.05	0.9	30	10	2.9	

Data taken from Popel and Johnson (2005) from the resting cat sartorius muscle, with data on haematocrit from Pries and Secomb (2008)

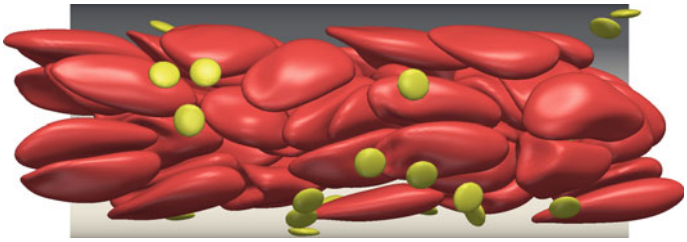

Fig. 8.3 Simulation of flow or red blood cells (RBCs) and platelets in a vessel with a diameter of 20 μm. Red cells are aligned with the direction of flow and there is a cell-free region near the wall. Platelets in *yellow* appear mainly in the cell-free region (having been pushed there by the RBCs). From; Rheologica Acta, Effect of tube-diameter and capillary number on platelet margination and near-wall dynamics, 2015, doi:10.1007/s00397-015-0891-6; Krüger T; © Springer-Verlag Berlin Heidelberg 2015, with permission of Springer

- *Variation of viscosity with vessel diameter*. Due to red cell depletion near the wall, the effective viscosity of the fluid is reduced when the vessel diameter is a few red blood cell diameters. Near the wall, the particle density is reduced and the viscosity is dominated by the underlying fluid. The viscosity mainly arises from flow in the high shear region near the wall, so that the overall viscosity is more akin to that of the fluid base rather than that of the suspension. This is called the Fahraeus–Linqvist effect after the authors of the original paper (Fahraeus and Lindqvist 1931). Calculations of the Fahraeus–Lindqvist effect shown in Fig. 3.15b demonstrate a minimum viscosity at a vessel diameter of around 7–9 μm depending on haematocrit. In smaller vessels the red blood cell is deformed and hence viscosity is higher.
- *Variation of haematocrit with vessel diameter*. This is concerned with reduction in haematocrit within the vessel compared to that within the receiving reservoir. This is called the Fahraeus effect after the author of the original paper (Fahraeus 1929). The explanation is similar for the Fahraeus–Lindqvist effect in that the red cells in the centre of the vessel move faster than the liquid at the edge of the vessel. Hence the relative volume of red cells to plasma is greater in the discharge fluid than for the fluid in the tube. Figure 3.15a shows that the effect is greatest (i.e. largest reduction in haematocrit) for a vessel diameter of 12–13 μm.
- *Red cell aggregation*. At low shear, red cells aggregate leading to an increase in viscosity and further exacerbating red cell depletion at the wall.

Building on the above understanding we will now look at a number of features of flow in the microcirculation. Further details of flow in the microcirculation are provided in review articles, e.g. Pries et al. (1996), Mchedlishvili and Maeda (2001), Baskurt and Meiselman (2003).

- *Plasma skimming*. This is the phenomenon whereby flow in a side-branch contains few or no red cells as a result of cell depletion at the wall of the parent vessel (Fig. 8.4). Through the microcirculation and in the capillary bed the red

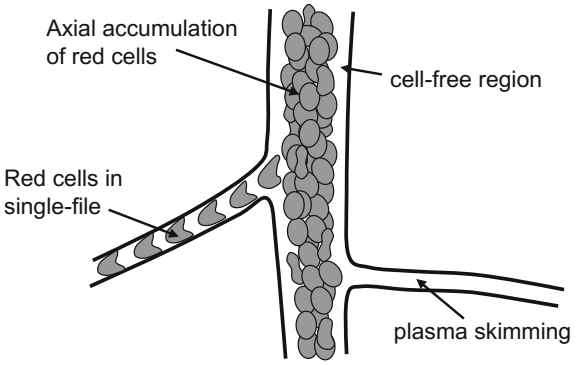

Fig. 8.4 Illustration of the flow of red cells in the microcirculation. There is a tendency to axially accumulate in the main vessel leading to a cell-free region near the wall. In one side-branch this leads to plasma skimming. In another branch red cells travel in single file

cell density will be highly variable depending on a number of factors including the diameter of the vessel, red cell aggregation and the flow rate.

- *Viscosity variations*. The effective viscosity is dependent on the red cell density, the diameter of the vessel, red cell aggregation, the flow rate and the exact path which is taken by the red cells through the microcirculation. These factors lead to considerable variation in viscosity in vessels of similar diameter, and variations in viscosity with diameter. Table 8.1 shows the highest viscosity of 15 mPa s for capillaries (compared to 3.5–4 mPa s in large arteries), and low viscosities of 2.8–2.9 mPa s in the large arterioles and venules.
- *Reduced and variable haematocrit*. The haematocrit (red cell concentration by volume) is 0.4–0.5 in the larger arteries and veins, with only a small variation in the value in different arteries and veins in the individual. In the microcirculation the haematocrit is reduced and has a wide variation in different vessels in the individual subject. Values of haematocrit are 0.29 ± 0.12 in arterioles, 0.23 ± 0.14 in capillaries and 0.31 ± 0.13 in venules (Pries and Secomb 2008).
- *Time dependence of haemodynamic quantities*. The effect of the passage of individual red cells will lead to variations of key quantities such as wall shear over short timeframes. This is at its most pronounced in the smallest vessels, the capillaries, where red cells traverse the capillary in single file.

8.2.3 Myogenic Effect and Bayliss Effect

The myogenic effect is the response of small arteries and arterioles to a change in blood pressure. Following an increase in blood pressure there is decrease in diameter caused by constriction of the smooth muscle cells in the media. Conversely; following a decrease in blood pressure there is an increase in diameter caused by relaxation of smooth muscle. This mechanism is locally controlled and is thought to be associated with a stretch-activated ion channel. This leads to depolarisation of the cells which in turn results in a calcium signal leading to muscle

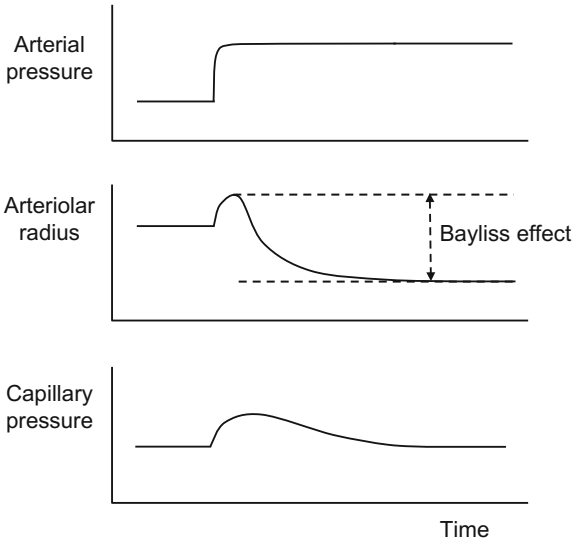

Fig. 8.5 Schematic of the myogenic effect in arterioles (Bayliss effect). A sudden change in blood pressure in an arteriole results initially in increase in diameter associated with passive elastic behaviour of the vessel wall. This is followed by constriction of the smooth muscle cells in the medial layer leading to decrease in diameter over a time period of 1–2 s. Capillary pressure increases following increase in arteriolar pressure but returns to baseline levels following arteriolar constriction

contraction. This effect was originally observed by Bayliss (1902) in arterioles where it is called the 'Bayliss effect'. The myogenic effect is also demonstrated in smaller arteries, especially intracerebral arteries. The Bayliss effect is the principle mechanism by which capillary pressure is maintained within a narrow range. The time course of the Bayliss effect is illustrated in Fig. 8.5. A sudden increase in blood pressure results in an initial increase in diameter as a result of the increased distending pressure. The increase in pressure is sensed by the smooth muscle cells in the media and there is calcium signalling leading to constriction of the smooth muscle cells. The constriction leads to decrease in the diameter. The initial increase in arteriolar pressure also leads to increase in capillary pressure. The decrease in arteriolar diameter is associated with increased resistance to flow, and hence increase in pressure drop across the arterioles. The increase in arteriolar pressure is therefore balanced by pressure loss and the capillary pressure is restored to its normal value.

8.2.4 Vessel Wall Mechanics

Studies on the pressure–diameter relationship of microvessels may be undertaken in excised vessels. In larger vessels, such as arteries, the blood pressure is much higher than the pressure in the surrounding tissue so the effect of the pressure on the vessel from the surrounding tissue can largely be ignored. This is not true in the microcirculation where the blood pressure is low. The overall pressure on the vessel wall is the 'transmural pressure' which is the difference between pressure acting on the wall from the inside (blood pressure) and the pressure acting on the wall from the

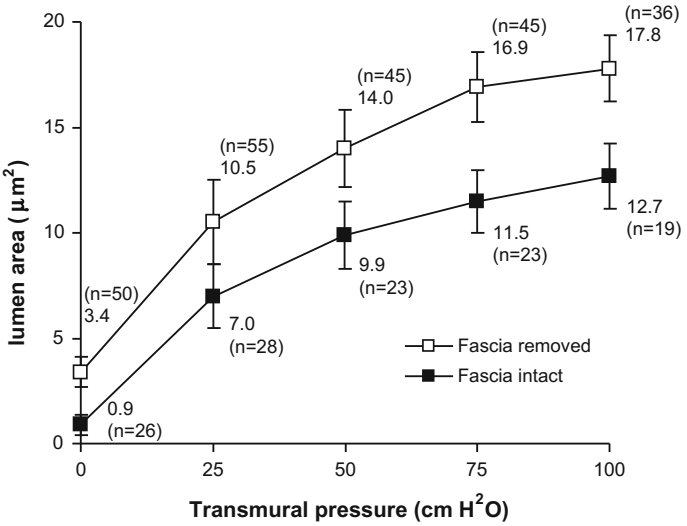

Fig. 8.6 Area-pressure in the capillary from the skeletal muscle of a rat. Average lumen area of the capillaries as a function of the capillary transmural pressure. The numbers indicate mean values (μm^2) and number of observations (*n*). Standard deviations are shown by the vertical bars. The capillary cross sections were derived from three muscles at each pressure. From; Annals of Biomedical Engineering, Biomechanics of skeletal muscle capillaries: hemodynamic resistance, endothelial distensibility, and pseudopod formation, volume 23, 1995, pp. 226–246; Lee J, Schmid-Schönbein GW; Copyright © 1995 Biomedical Engineering Society, with permission of Springer

outside and experimental data in this area is often presented in terms of transmural pressure. In general a non-linear relationship is exhibited between transmural pressure and diameter, similar to that seen in larger vessels. Figure 8.6 shows area as a function of transmural pressure for capillaries showing a non-linear relationship in which incremental distension reduces as pressure increases. Figure 8.7 shows the corresponding stress–strain curve calculated using a simple elastic model; it can be seen that the stress–strain behaviour also exhibits a non-linear relationship.

For microvessels which have muscular tone (i.e. where the smooth muscle cells cause constriction), the pressure–diameter behaviour has both an active and a passive component (Fig. 8.8). The passive component corresponds to the artery with smooth muscle cells in a state of maximum relaxation. The active component is dependent on vascular tone; i.e. on the level of contraction of the smooth muscle.

In the arterial system it was noted that the elastic nature of the vessel wall gave rise to pressure wave propagation, with the speed referred to as the ‘pulse wave velocity’ or PWV. The compliant nature of microvessels also leads to pressure wave propagation. Values of PWV in the range 3.5–134 cm s^{-1} were found in

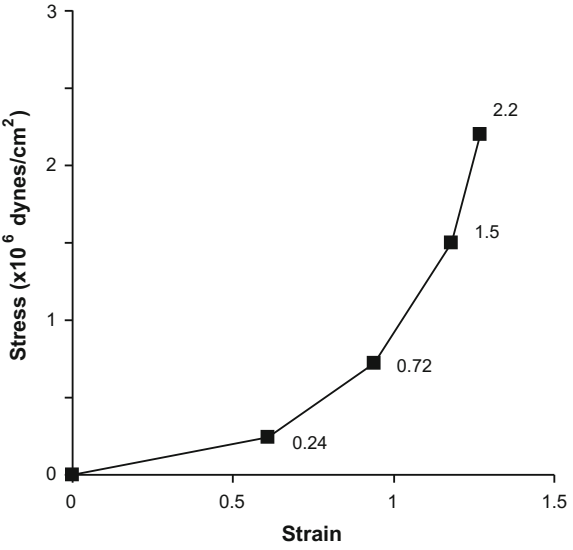

Fig. 8.7 Capillary stress–strain behaviour from the skeletal muscle of a rat. Average circumferential stress–strain curve for isolated capillaries without the wall support provided by surrounding skeletal muscle fibres. From; Annals of Biomedical Engineering, Biomechanics of skeletal muscle capillaries: hemodynamic resistance, endothelial distensibility, and pseudopod formation, volume 23, 1995, pp. 226–246; Lee J, Schmid-Schönbein GW; Copyright © 1995 Biomedical Engineering Society, with permission of Springer

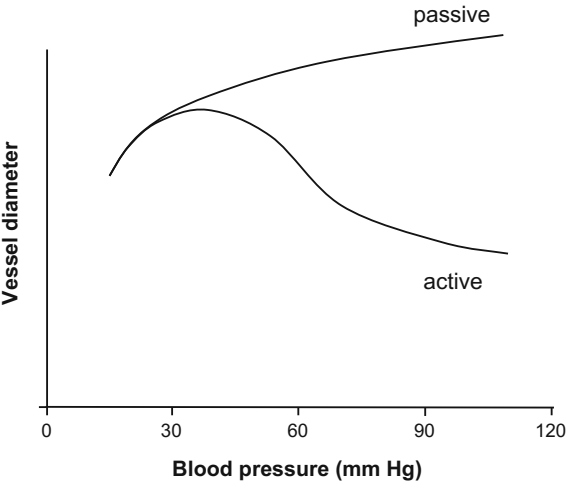

Fig. 8.8 Schematic diagram showing the pressure–diameter relationship in the arteriole when the smooth muscle is relaxed (*passive*) and constricted (*active*)

arterioles of diameter 12–43 μm, with PWV increasing with diameter (Seki 1994). Using acoustic microscopy, Yeh et al. (2012) found mean values of PWV in arterioles of 30 cm s^{-1} (30 μm diameter) increasing to 110 cm s^{-1} (60 μm diameter). For pulse propagation in the capillary, a value of about 10 cm s^{-1} was estimated by Caro et al. (1978).

8.2.5 Vasomotion

Vasomotion describes the cyclic variation of vessel tone which is unrelated to the heart beat or to respiration. It has been observed that arterioles may exhibit regular changes in diameter at a frequency of 3–30 min^{-1}. The total change in diameter during vasomotion is large at 50–100 % of the mean diameter (Tuma et al. 2008). The changes in diameter are linked to contraction and relaxation of the smooth muscle in the medial layer of the vessel wall. The function of this motion is uncertain but several possible benefits of vasomotion have been described (Arciero and Secomb 2012): reduction in hypoxia in resting muscle, improved oxygenation and blood flow in tissues adjacent to muscle, improved filtration through the vessel wall, and improved lymphatic drainage.

A model of vasomotion was developed by Gonzalez-Fernandez and Ermentrout (1994) which predicts its main features. Central to this model is the myogenic effect. The model itself is complex but the key feature involves polarisation of the cell membrane which, as noted above, leads to muscle call contraction. Calcium influx leads to polarisation hence to vessel constriction. Potassium influx repolarises the membrane leading to muscle relaxation. A delay between calcium influx and potassium influx will lead to oscillations in the contraction of the smooth muscle, and hence to oscillation in diameter. Other theories are explored by Secomb (2008).

8.2.6 Flow Pulsatility

Flow pulsatility in the microcirculation arises from several sources which are described in this section:

- *Arterial pressure pulsation*. Arteries have a high degree of flow-related pulsatility. This variation is damped within the arteriolar system and it was long assumed there was no transmission of this flow pulsatility to the capillaries. In other words, one of the functions of the arteriolar bed is to damp the pressure variation arising from the heart and to produce steadier flow in the capillaries. However, it has been shown that flow may be pulsatile in the most distal arterioles with some component of this pulsatility arising from the undamped blood pressure wave from upstream arteries.
- *Myogenic effect*. The variations in arteriolar diameter described above will lead to some variation in blood velocities.
- *Tissue compression*. Changes in pressure within the tissues will lead to changes in transmural pressure which will affect vessel cross-sectional area and hence blood velocity.

8.2.7 *Wall Stress and Adaptability*

Wall shear stress (WSS), the viscous drag of the blood on the vessel wall, has been estimated in the microcirculation using both measurement and simulation. The WSS will depend on diameter of the vessel, the flow rate and on the blood characteristics near the wall. It is noted that in much of the microcirculation there is depletion of red cells at the vessel wall so that haematocrit and viscosity are reduced near the wall. These will impact on WSS (reduced viscosity at the wall leads to reduced WSS, reduced haematocrit at the wall leads to increased WSS). In addition, the passage of individual red cells will give rise to time-varying WSS. Early experimental measurements of WSS are presented in Fig. 8.9. These show high values in the arterial side of the microcirculation with much reduced values in the venous side.

In Chap. 5 it was discussed that WSS is a key feature of a control mechanism involving the endothelium, in which arterial diameter is adjusted in order to maintain mean WSS within a narrow range. Figure 8.10a shows WSS as a function of diameter and Fig. 8.10b shows WSS as a function of pressure. In terms of a control mechanism, Pries and Secomb (2008) suggest that a simple Murray's law model of design (based on minimisation of energy leading to independence of WSS with diameter; see Chap. 5) is inappropriate for the microcirculation, but that there is an adaptation process common to all types of vessel involving both wall shear stress and pressure.

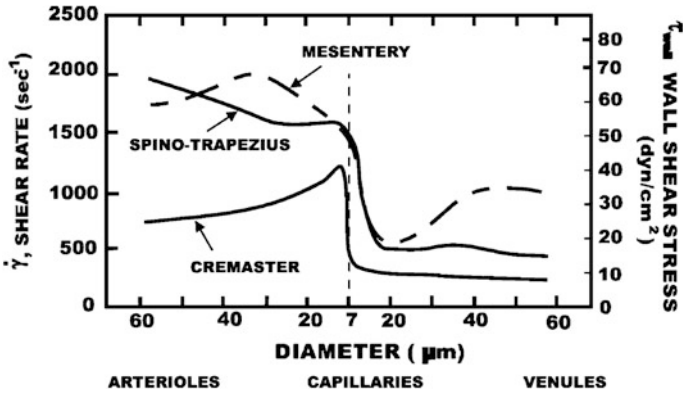

Fig. 8.9 Shear rate and wall shear stress in the microcirculation. Representative arteriovenous distributions of shear rate and wall shear stress from measurements of red cell velocity in the microcirculation of mesentery, spinotrapezius muscle and cremaster muscle. Vessel diameter (abscissa) may be considered as an index of position with the network. Values of wall shear stress were estimated from the product of shear rate and viscosity assuming a viscosity value of 3.5 mPa s. From; Flow-Dependent Regulation of Vascular Function; Shear Stress in the Circulation; 1995, pp. 28-45, Lipowsky HH, Copyright © 1995 by the American Physiological Society, with permission of Springer

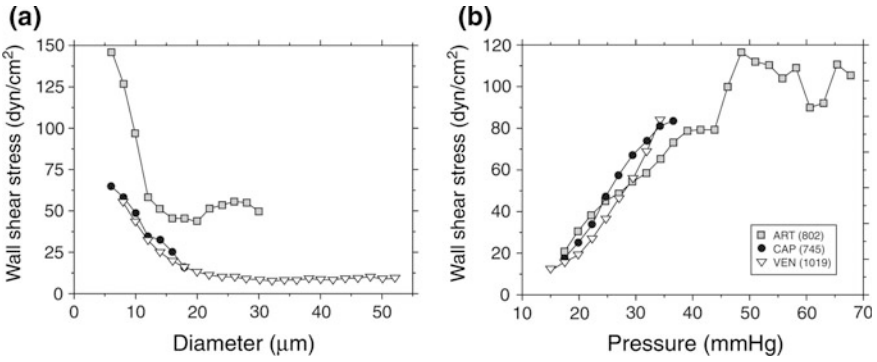

Fig. 8.10 Wall shear stress for arterioles, capillaries and venules as a function of **a** diameter and **b** pressure. Reprinted from Handbook of Physiology: Microcirculation. 2nd ed; Blood flow in microvascular networks; Pries AR, Secomb TW; with permission from Elsevier; pp. 3–36, copyright (2008); with permission from Elsevier

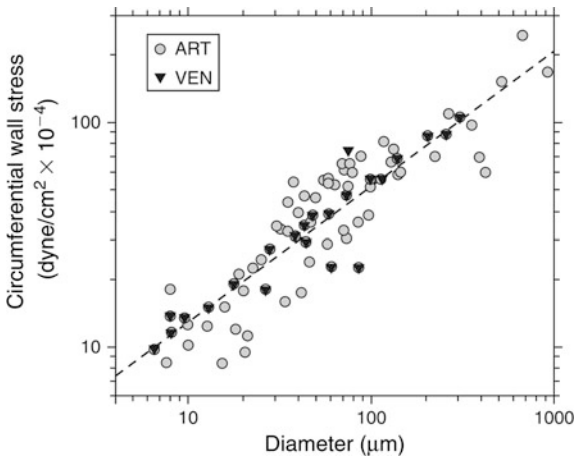

Fig. 8.11 Circumferential wall stress in vessels as a function of diameter. Reprinted from Handbook of Physiology: Microcirculation. 2nd ed; Blood flow in microvascular networks; Pries AR, Secomb TW; with permission from Elsevier; pp. 3–36, copyright (2008); with permission from Elsevier

Pries and Secomb (2008) also showed that circumferential stress and vessel diameter are linearly related (Fig. 8.11) suggesting a similar adaptation process common to all vessels.

Following from the above, it is relevant to discuss the relationship between mechanical forces and adaptability (remodelling) of the microcirculation. Secomb and Pries (2011) summarise that the same principles that occur in the larger arteries apply, but with some modifications. In arteries (Chap. 5), the three main

relationships are: wall shear stress and diameter, circumferential stress (related to pressure) and wall thickness, and longitudinal stress and longitudinal length. In addition Secomb and Pries (2011) describe that metabolic demand is a key determinant of vascular structure in the microcirculation.

Microcirculation adaptability also involves the generation of new vessels, a process which is referred to as angiogenesis. As the tissues of the body are under constant change, angiogenesis is an ongoing process which occurs every day. For example, exercise will increase skeletal muscle mass requiring the production of new vessels. Similarly, the increase in adipose (fat) tissue associated with weight gain will also be associated with the development of new vessels and injury is followed by repair and the laying down of new tissue and a new microcirculation. Many diseases are associated with the development of a new microcirculation, especially cancer where the growing tumour establishes its own blood supply.

8.3 Molecular Transport

While the heart and larger vessels are involved in transport of blood from one part of the body to another, the main transport function of the microcirculation concerns the exchange of molecules between the blood and the tissues of the body. This section describes the main transport mechanisms. Most molecular transport involves the diffusion of molecules, in which the delivery of oxygen to the tissues is a key function. Oxygen is a key molecule required for metabolic processes. Within the body the diffusion distance for oxygen is found to range from 20 to 200 μm. This variation is closely linked with metabolic demand; shorter diffusion distances are required for tissues with high metabolic activity such as skeletal muscle during exercise, and longer distances are observed for tissues with low metabolic activity. Most tissues in the body are within about 100 μm of a capillary, presumably in order to ensure adequate delivery of oxygen to tissues.

8.3.1 Starling's Equations

Starling's equation (Eq. 8.1) is concerned with the absorption and filtration of molecules across the capillary wall. Water is able to flow freely from the blood into tissues through small gaps ('tight junctions' or fenestrations, depending on the type of capillary) in the endothelium. The net flow rate depends on the balance between the hydrostatic pressure and the colloid osmotic pressure (also known as the oncotic pressure) within the capillary (Fig. 8.12). Remembering that pressures in the microcirculation are low and that the tissues may be under some form of pressure due to external or internal compression, the net hydrostatic pressure is the difference between the blood pressure and the pressure in the surrounding tissues. The colloid osmotic pressure derives from the presence of proteins in the blood. The most

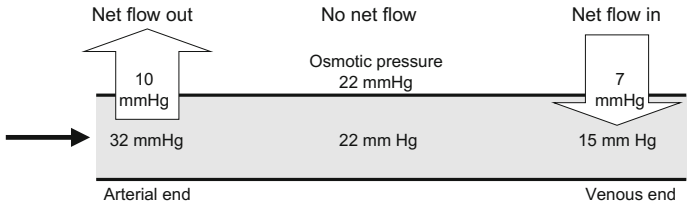

Fig. 8.12 Relationship between blood pressure, osmotic pressure and flow in the capillary

important protein in this respect is albumin. Water diffuses freely across a porous membrane and there will be a net flow from higher to lower concentrations. As the percent by volume of water is less in blood than in the surrounding tissues there is a net tendency for water to diffuse into the capillary. The additional intravascular pressure which would need to be applied to the blood to stop diffusion is called the 'colloid osmotic pressure'. The two relevant pressures influencing the diffusion of water from the capillaries to the surrounding tissues are therefore:

- *net hydrostatic pressure*: difference between pressure p_c in the blood and the pressure p_i in the interstitial fluid, and
- *net colloid osmotic pressure*: difference between osmotic pressure π_c in the blood and the osmotic pressure π_i in the interstitial fluid.

Starling's equation describes trans-capillary flow Q as follows:

$$Q = K_f([p_c - p_i] - [\pi_c - \pi_i]), \tag{8.1}$$

where K_f is the filtration coefficient (a constant related to the area available for exchange and the capillary wall permeability).

When the net hydrostatic pressure exceeds the net osmotic pressure, which is the situation at the entrance region of the capillary, water will flow from the capillaries into the surrounding tissue. Conversely when the net hydrostatic pressure is less than the net osmotic pressure, water will flow from the surrounding tissues into the capillary. This situation applies at the exit region of the capillary.

The flow of fluid into or out of the capillaries requires that the blood pressure at the level of the capillary is maintained at a stable level. It was noted above that the myogenic effect has a major role to play in maintaining constant blood pressure in the capillaries.

8.3.2 Molecular Movement Across the Capillary Wall

The molecules present within blood which move across the capillary wall are: water; gases such as CO_2, O_2 and NO; electrolytes such as Na^+ and K^+; and various larger molecules such as glucose, amino acids and hormones. There are three main

methods for movement of molecules across the capillary wall which will be described in this section. Further details may be found in Popel and Pittman (2014).

Diffusion. Diffusion concerns movement of molecules down a concentration gradient. Both CO_2 and O_2 are lipid soluble so can diffuse from the blood to the extracellular space across the lipid bilayer of the endothelium. Larger molecules such as steroid hormones can also diffuse by this method. In contrast, water-soluble molecules diffuse through gaps (fenestrations or larger pores) in the capillary wall. Examples of water-soluble molecules are glucose and amino acids.

Vesicular transport. A vesicle is a fluid-filled structure formed from the membrane of the cell (lipid bilayer). The vesicle is formed on one side of the endothelial cell (e.g. on the luminal side, adjacent to the blood) and moves across to the other side (e.g. on the side adjacent to the basement membrane). The vesicle and its contents are transported across the endothelium. This mode of transport is important for larger molecules such as antibodies that are unable to diffuse readily due to size or lack of lipid solubility.

Bulk flow. The mechanisms concerning bulk flow have been described above under 'Starling's law'. Bulk flow occurs through pores and clefts and is particularly important in fenestrated and sinusoidal capillaries.

8.4 Control of Flow

A simple model of the arterial system from heart to capillaries relating flow, pressure and resistance was described in Chap. 4. It was noted that changes in local flow are mainly effected through changes in arteriolar resistance, achieved by alteration of vessel diameter. Arterioles are vasoactive in that they have smooth muscle which when contracted leads to decrease in vessel diameter and conversely, when relaxed leads to increase in diameter. Some arterioles are capable of constriction to the point of complete shut down of flow. This large range of variation in diameter allows considerable change in local resistance which in turn allows for large variations in local flow rate. For example, in skeletal muscle under exercise, or following release of a tourniquet (where it is called reactive hyperaemia), there is an increase in flow rate by a factor of up to 20.

The ability of the microcirculation to maintain constant perfusion over a wide range of input pressure is referred to as blood flow autoregulation. Figure 8.13 shows schematically the effect of changing arterial pressure on perfusion. At low pressure, arterioles are fully dilated in an attempt to maximise the flow rate. Conversely, at high pressure arterioles are maximally constricted in order to keep the flow rate down. Between these two regions arterioles can constrict/dilate as necessary in order to maintain perfusion within a narrow range.

The factors involved in control of local flow rate are metabolic control, shear stress control and myogenic control and are described below. Further reading is provided by Carlson et al. (2008) and Secomb (2008). These control mechanisms interact which is considered in the model of flow autoregulation described by

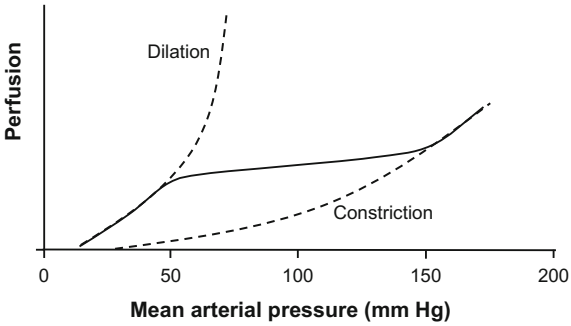

Fig. 8.13 Schematic of flow autoregulation; showing perfusion plotted against mean arterial pressure

Carlson (2008). Their model, incorporating all three control mechanisms, was able to reproduce the experimentally observed dependence of perfusion on mean arterial pressure.

8.4.1 Metabolic Control

Two of the main functions of the microcirculation are to ensure sufficient supply of oxygen to the tissues for metabolic purposes, and to remove the waste products of metabolism such as carbon dioxide. Local control of blood flow to tissues is initiated by changes in the concentration of oxygen and carbon dioxide in tissues which leads to changes in arteriolar constriction. A decrease in oxygen concentration (occurring as a result of increased metabolism; e.g. muscles at work) leads to arteriolar smooth muscle relaxation and increase in local perfusion. Carbon dioxide has a similar effect in that an increase in CO_2 concentration leads to an increase in local perfusion. For oxygen, the actual mechanism was initially thought to be detection of oxygen concentration at the level of the arteriole but this appears not to be the case. Instead changes in oxygen concentration are detected downstream, possibly at the level of the venules, and information is communicated to the arterioles through cell–cell signalling along the vessel walls via gap junctions (Secomb 2008; Pries and Secomb 2008).

8.4.2 Shear Stress Control

Endothelium responds to changes in wall shear stress as discussed above and in Chap. 5. Increased shear stress is associated with release of NO which is a potent vasodilator, resulting in smooth muscle relaxation and increase in diameter in an attempt to normalise wall shear stress. As with metabolic control it is thought that the wall shear stress is detected downstream and that cell–cell signalling results in dilation at the level of the arterioles (Pries and Secomb 2008).

8.4.3 Myogenic Control

In Sect. 8.2.3 above it was noted that the myogenic effect is concerned with the change in arteriolar diameter arising from a change in pressure, and that this is the principle mechanism by which capillary inlet pressure is maintained constant. There will be associated changes in flow rate arising from a change in pressure; the flow rate will initially increase due to the raised pressure then normalise as the myogenic effect occurs.

References

Aarts PAMM, van den Broek SA, Prins GW, Kuiken GDC, Sixma JJ, Heethaar RM. Blood platelets are concentrated near the wall and red blood cells, in the center in flowing blood. Arteriosclerosis. 1988;8:819–24.

Arciero JC, Secomb TW. Spontaneous oscillations in a model for active control of microvessel diameters. Math Med Biol. 2012;29:163–80.

Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. Semin Thromb Hemost. 2003;29:435–50.

Bayliss N. On the local reactions of the arterial wall to changes of internal pressure. J Physiol. 1902;28:220–31.

Carlson BE, Arciero JC, Secomb TW. Theoretical model of blood flow autoregulation: roles of myogenic, shear-dependent, and metabolic responses. Am J Physiol Heart Circ Physiol. 2008;295:H1572–1579.

Caro CG, Pedley TJ, Schroter RC, Seed WA. The mechanics of the circulation. Oxford: Oxford University Press; 1978. p. 383.

Fahraeus R. The suspension stability of the blood. Phys Rev. 1929;9:241–74.

Fahraeus R, Lindqvist T. The viscosity of the blood in narrow capillary tubes. Am J Physiol. 1931;96:562–8.

Gonzalez-Fernandez JM, Ermentrout B. On the origin and dynamics of the vasomotion of small arteries. Math Biosci. 1994;119:127–67.

Mchedlishvili G, Maeda N. Blood flow structure related to red cell flow: determinant of blood fluidity in narrow microvessels. Jpn J Physiol. 2001;51:19–30.

Popel AS, Pittman RN. The microcirculation physiome. In: Peterson DR, Bronzino JD, editors. Biomechanics—principles and practices. Boca Raton: CRC Press; 2014. p. 13-1–13-18.

Popel AS, Johnson PC. Microcirculation and Hemorheology. Annu Rev Fluid Mech. 2005;37:43–69.

Pries AR, Secomb TW. Blood flow in microvascular networks. In: Tuma RF, Duran WN, Ley K, editors. Handbook of physiology: microcirculation. 2nd ed. San Diego: Academic Press; 2008. p. 3–36.

Pries AR, Secomb TW, Gaehtgens P. Biophysical aspects of blood flow in the microvasculature. Cardiovasc Res. 1996;32:654–67.

Secomb TW. Theoretical models for regulation of blood flow. Microcirculation. 2008;15:765–75.

Secomb TW, Pries AR. The microcirculation: physiology at the mesoscale. J Physiol. 2011;589:1047–52.

Segre G, Silberberg A. Behaviour of macroscopic rigid spheres in Poiseuille flow. Part 2. Experimental results and interpretation. J Fluid Mech. 1962;14:136–57.

Seki J. Flow pulsation and network structure in mesenteric microvasculature of rats. Am J Physiol. 1994;266:H811–21.

Tuma RE, Duran WN, Ley K. Handboook of physiology: microcirculation. San Diego: Elsevier; 2008.

Yeh C, Hu S, Maslov K, Wang LV. Photoacoustic microscopy of blood pulse wave. J Biomed Opt. 2012;17:070504. doi:10.1117/1.JBO.17.7.070504.