Chapter 3
Blood and Blood Flow

Peter R. Hoskins and David Hardman

Learning outcomes

1. Describe the constituents of blood and discuss their function.
2. Describe the main forces acting on blood particles.
3. Describe the Segre-Silberberg effect and discuss its origin in terms of forces.
4. Describe Rouleaux formation and discuss its origin in terms of forces.
5. Describe leukocyte adhesion and discuss the role of forces in adhesion.
6. Discuss the effect of particle deformability on the viscosity—volume fraction curve.
7. Describe the role of spectrin in maintaining red cell shape.
8. Describe the effect of shear rate on the shape of the individual red cell.
9. Describe the shape of red cells when flowing in tubes of different diameter.
10. Describe the viscosity–wall shear rate curve for whole blood.
11. Discuss the shape of the viscosity–wall shear rate curve for whole blood in terms of red cell behaviour.
12. Describe the Fahreaus effect and the Fahraeus–Linqvist effect.
13. Discuss the Fahreaus effect and the Fahraeus–Linqvist effect in particle depletion at the wall.
14. Describe and discuss the viscous behaviour of blood in arteries.
15. Describe the viscous behaviour of blood in the heart, veins and microcirculation.

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Blood is the fluid which flows in the cardiovascular system. It is, however, not a pure fluid but rather a suspension of a number of different particles (cells, cell fragments and macromolecules) in a fluid base. This chapter explores the fluid behaviour of blood including the impact of the particles on this behaviour. The study of blood flow has developed over many decades and blood rheology continues to be a highly active area of research. Ideally knowledge would be based on data collected in vivo, however, this is difficult to obtain. In practice, an understanding of blood rheology is obtained from many sources; the general area of flow of particle suspensions (important in other areas such as microfluidics and transport of chemicals), experiments involving particles which simulate blood cells, in vitro and in vivo observations and computational modelling. In the absence of definitive in vivo data this chapter draws on all of these sources to help create understanding of blood and blood flow.

3.1 Constituents of Blood

The constituents of blood are considered in this section and include the fluid base 'plasma' and a number of particles listed in Table 3.1. Figure 3.1 shows a 'blood smear' which shows blood cells from a sample of human blood photographed using an optical microscope.

3.1.1 Plasma

Plasma is a straw coloured fluid and consists of 90 % water and 1 % electrolytes, with various molecules making up the remainder. Electrolytes play an important role in ensuring the correct fluid content within cells; consequently, electrolyte concentration is subject to several control mechanisms. Low plasma volume may arise from a number of causes including dehydration, salt depletion (e.g. following sport), or blood loss. High plasma volume can occur as a result of inadequate salt excretion associated with kidney disease.

3.1.2 Macromolecules and Other Molecules

Macromolecules make up around 9 % of the plasma volume. The majority of molecules are proteins, such as globulins (part of the immune system), albumin (important for maintenance of oncotic pressure) and fibrinogen (part of the clotting system). Also present are a number of molecules in transit such as vitamins, hormones, waste products (urea, ammonia), carbon dioxide and oxygen. After a meal there is an increase in volume of fatty acids, amino acids and peptides arising from

Table 3.1 Components of blood

Blood component	% By volume	Principle function	Low %volume	High %volume
Plasma	50–60	Fluid base for blood, carbon dioxide and nutrient transport	Dehydration Blood loss Excess salt loss (e.g. after sport)	Kidney disease
Red cells	40–50	Carrying oxygen	Blood loss Sickle cell anaemia Enlarged spleen Cancer	Polycythaemia Chronic hypoxia Blood doping Dehydration
White cells	0.7	Immune system	Medication and radiation treatment Immune dysfunction (e.g. AIDS) Toxins including alcohol Major surgery	Infection (normal) Genetic disorders Leukaemia Spleen removal
Platelets	0.3	Clotting of blood	Medication and chemotherapy HELLP syndrome Haemolytic-uremic syndrome Snakebite	Thrombocytosis
Macromolecules: albumin	2	Maintenance oncotic pressure	Reduced production (various diseases)	Dehydration
Other	1.5	Various		

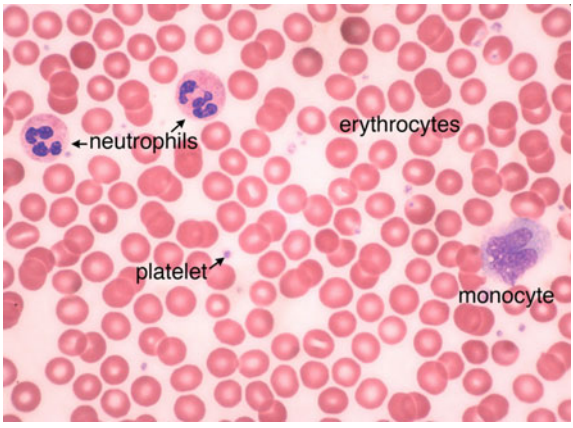

Fig. 3.1 Blood cells. Several types of blood cells are shown including red cells (erythrocytes), two different white cells (neutrophils and a monocyte) and platelets. Image kindly provided by Karen Hart, Peninsula College, Port Angeles, WA, USA. © 2006–2010 Karen Hart

digestion in the blood. Some of these molecules such as LDL (low density lipoprotein) cholesterol play important roles in arterial disease.

Albumin is important in regulating the balance of fluids in the body. Low levels of albumin in blood are due to lack of protein in the diet or due to impaired production from the liver or to kidney disease. Low albumin levels result in an imbalance of fluids resulting in generalised swelling of tissues as a result of water retention, known as 'oedema'. A high level of albumin may arise from excess protein in the diet, but are usually caused by dehydration where the fluid levels in the tissues are low.

3.1.3 Red Cells

The principle particle in blood is the red cell or erythrocyte. The percent by volume of red cells is called the haematocrit, the packed cell volume or the erythrocyte volume fraction. The haematocrit has a normal range of 41–52 % in men and 36–48 % in women. The red cell is unique as, unlike other cells it has no nucleus and it has a biconcave shape (Fig. 3.2). Human red cells, have a diameter of 7.5 μm, a thickness of 2.0 μm and an effective diameter (i.e. the diameter if the red cell

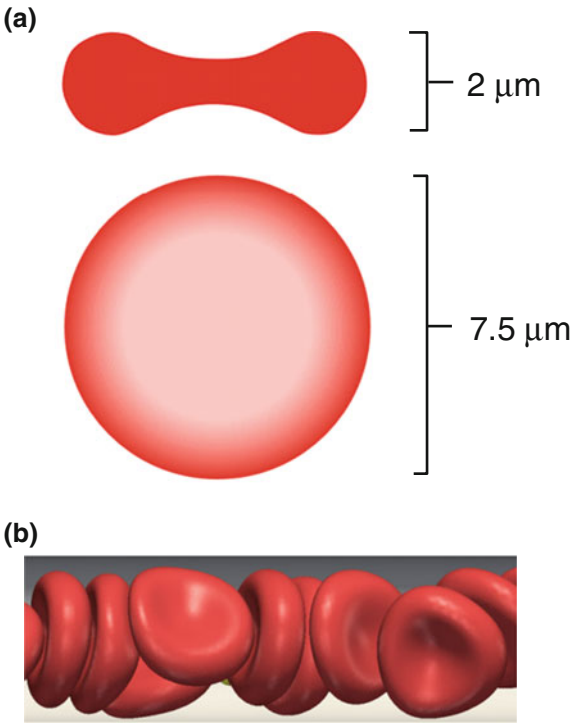

Fig. 3.2 Red cells. **a** Red cell shape and dimensions. **b** Red cells at low shear. (**b**) from; Krüger (2015); © Springer-Verlag Berlin Heidelberg 2015, with permission of Springer

contents were formed into a sphere) of 5.5 μm. The size and shape of red cells is remarkably similar across all mammals; the diameter of a red cell in a mouse and an elephant is about the same. Red cells are involved in the transport of oxygen from the lungs to the tissues, for which the iron in the red cell plays an important role. Low haematocrit has a number of causes, including blood loss and various diseases. High haematocrit leads to an increase in the oxygen carrying ability of the blood, which is the reason why some athletes involved in endurance events have blood transfusions before the race. However it is also risky, as the viscosity of blood is higher, leading to greater resistance to flow and increased risk of clinical events such as heart attack and stroke. Sickle cell disease is associated with abnormally shaped red cells in the form of a sickle rather than a disc. While the oxygen carrying capability is impaired, the presence of sickle cells gives immunity against malaria, a deadly disease which operates through destruction of red cells.

3.1.4 White Cells

White cells, or leukocytes, occupy some 0.7 % of the blood volume in health. There are a number of different leukocytes as shown in Fig. 3.3, each with a different role. Neutrophils (diameter 10–12 μm) ingest and digest bacteria and fungi. Eosinophils (diameter 10–12 μm) attack larger parasites and are involved in allergic responses. Monocytes (diameter 15–30 μm) are carried by the cardiovascular system to different tissues where they transform into cells called macrophages. Lymphocytes (diameter 7–15 μm) attack invading bacteria and viruses and also help destroy cells

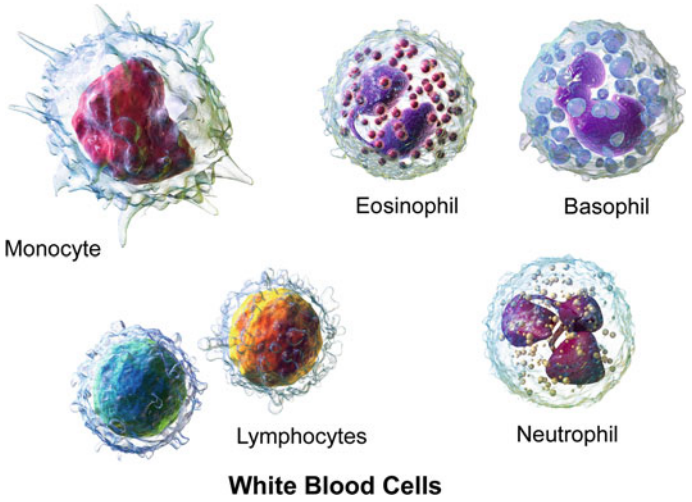

Fig. 3.3 White cells; illustration of various types of white cell. Image reproduced from wikipedia with permission. Original image authored by Bruce Blausen: Wikiversity Journal of Medicine. doi:10.15347/wjm/2014.010. ISSN 20018762.—Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28223981

in the body which have become diseased through virus infection or cancer. Basophils (diameter 12–15 μm) are involved in response to allergic symptoms including histamine release. An increase in the volume fraction of white cells is a normal response to infection and is not usually harmful. However abnormal increases occurring in diseases such as leukaemia may be fatal. Low white cell volumes are due to decreased production or increased destruction arising from various diseases and lead to impaired functioning of the immune system.

3.1.5 Platelets

Platelets are fragments of much larger cells called megakaryocytes and occupy 0.3 % of the blood volume in health. Platelets exist in unactivated and activated forms (Fig. 3.4). The majority of circulating platelets are unactivated and their shape is plate-like (hence the name 'platelet'). These have a greatest diameter of 2–3 μm. Once activated, they become sticky and more spherical with projections (pseudopods). These projections are important in enabling activated platelets to clump together. Platelets are involved in blood clotting and in the repair of damaged endothelium. If the endothelium is damaged, underlying collagen fibres are exposed. Unactivated platelets coming into contact with collagen become activated and will stick to the collagen sealing off the damaged area after which repair of the area ensues. Platelets can also be activated by increases in wall shear in narrowed vessels. Low platelet volume fraction can arise from a number of diseases and lead

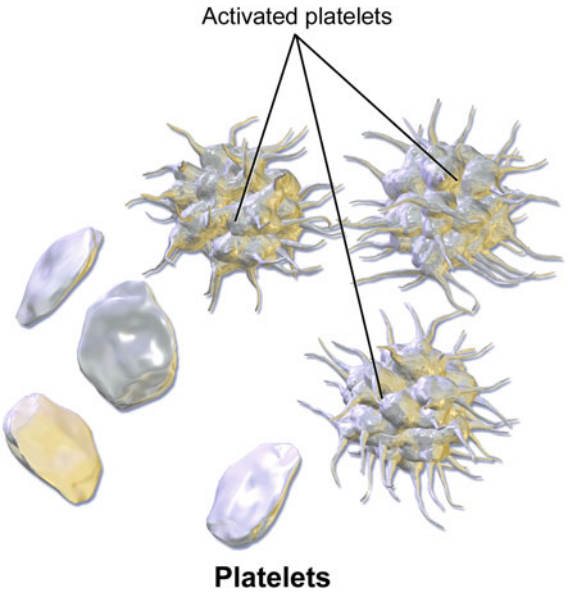

Fig. 3.4 Platelets; illustration of unactivated and activated platelets. Image reproduced from wikipedia with permission. Original image authored by Bruce Blausen: Wikiversity Journal of Medicine. doi:10.15347/wjm/2014.010. ISSN 20018762.—Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=28223979

to impaired clotting ability, leading to potentially life-threatening blood loss from minor wounds. Increased platelet volume fraction arising from disease leads to increased risk of thrombosis which in turn may lead to potentially life-threatening clinical events such as heart attack and stroke.

3.2 Forces on Blood Particles

This section examines the forces on particles and discusses these in the context of blood viscosity and blood flow. The examples below are drawn from a variety of sources including in vitro experimental flow systems, computational modelling and in vivo measurements.

3.2.1 Forces Associated with Gravity

Gravity is a long-range force affecting all particles in a fluid in the lab and in the human body on planet earth (and any other planet or moon humans choose to live on). The forces on a particle arising from gravity are:

- *Gravitational force*. The weight of the particle will tend to make the particle fall in a gravitational field.
- *Buoyant force*. The hydrostatic pressure (difference in pressure in the fluid due to height difference) tends to make the particle rise in a gravitational field.

These forces are illustrated in Fig. 3.5. If the particle density is greater than the fluid density then the overall force will cause the particle to sink. Conversely if the particle density is less than the fluid density, then the particle will rise. When the particle density is the same as the density of surrounding fluid, there is no net force on the particle and the particle is said to be 'neutrally buoyant'. The density of an average red

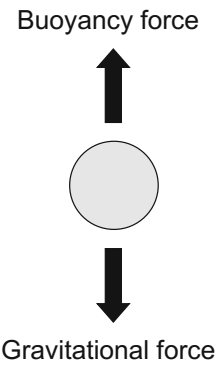

Fig. 3.5 Forces on a particle initially at rest in a stationary fluid

cell, at 1125 kg m^{-3}, is slightly higher than that of plasma at 1025 kg m^{-3}, and so red cells have a slight tendency to sink.

3.2.2 *Forces Associated with the Velocity and Shear Field at High Reynolds Number*

Forces arising from the velocity and shear field have different effects depending on the flow conditions in the vessel. In the following sections the forces will be based on Reynolds number. It will be recalled that Reynolds number (*Re*) is the ratio of inertial to viscous forces. Effects due to inertia of the fluid (present at high *Re*) are most prevalent in larger vessels and will be considered in this section. Effects relevant at lower *Re* (<1) where viscous forces dominate, are most prevalent in the microcirculation and will be considered in the next section. Figure 3.6 shows the principal forces arising from motion of the fluid. The forces are as follows:

- *Drag force*. When there is relative motion between the fluid and the particle, the particle experiences a force in the direction of the flow as a result of the inertia of the particle. If a fluid is at rest and is subject to a pressure gradient, the fluid will accelerate. The particle experiences a force in the direction of the fluid motion which accelerates the particle until there are no forces in the direction of

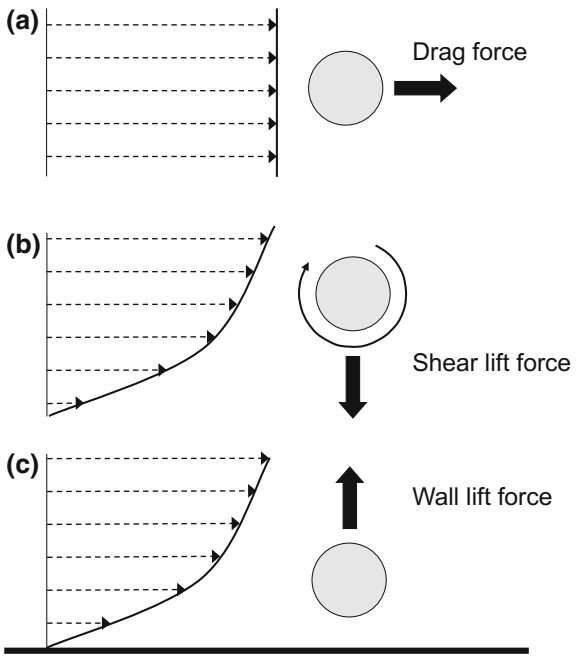

Fig. 3.6 Inertial forces arising from motion of the fluid with respect to the particle. **a** Drag force. **b** Shear induced lift. **c** Wall induced lift. Note that lateral motion of the particle will also give rise to a drag force

motion. If there is lateral motion of the particle (i.e. across streamlines) then this relative motion will also lead to a drag force.

- *Shear-induced inertial lift*. When a particle is in a shear field the difference in shear on either side of the particle causes the particle to spin. There is an associated force perpendicular to the direction of fluid motion which causes the particles to migrate to higher shear rate regions. The force originates from inertial effects in the fluid surrounding the particle. Ho and Leal (1974) provided one of the first theoretical formulations which gave good agreement with experimental data.
- *Wall-induced inertial lift forces*. A number of different inertial forces are present on a particle near a wall or a particle touching a wall. All these forces are directed away from the wall leading to motion of the particle away from the wall. These include lift on a non-spinning particle near a wall (Cherukat and McLaughlin 1994), lift on a spinning particle near a wall (called the Magnus effect), and lift on a particle touching the wall (Leighton and Acrivos 1985).

In 1962, Segre and Silberberg published a paper on flow of neutrally buoyant solid particles in a vertical tube. The particles were uniformly distributed at the inlet to the tube but, further along, they located in a ring of particles at a distance of 0.6 of the tube radius from the centre. This was termed the 'tubular pinch effect' and subsequently became known as the Segre-Silberberg effect. The pinch effect was strongest for *Re* numbers of less than about 30. For higher *Re* the width of the particle-free region near the wall increased and there was spreading of the particles throughout the whole cross section of the tube. The explanation for this effect concerns inertial forces which push the particle across the streamlines (di Carlo 2009). Particles experience a shear-induced lift force which pushes the particles away from the centre. Particles near the wall experience a lift force as a result of the presence of the wall which pushes them away from the wall. The particles locate at a distance where these 2 forces balance each other (Fig. 3.7). At higher Reynolds numbers, the balance of lift forces changes and the equilibrium position moves towards the wall. Higher Reynolds number flows of 500–2000 is associated with an inner annulus and a more uniform distribution (Matas and Morris 2004). These effects are seen at low volume concentrations, less than 20 %, where particle–particle interaction can be neglected. However, any particle suspension at $Re > 1$ will be subject to these lift forces to some degree, which will lead first, to particle depletion at the wall and second, to inhomogeneity in particle concentration.

3.2.3 *Forces Associated with the Velocity and Shear Field at Low Reynolds Number*

At low Reynolds numbers < 1, flow is dominated by viscous effects. Forces arising from inertial effects, such as the lift forces discussed in Sect. 3.2.2, do not occur. A formal explanation for this is that at very low *Re*, fluid flow is governed by

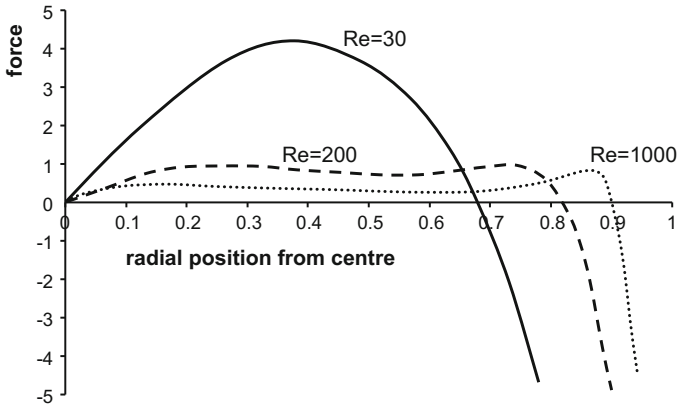

Fig. 3.7 Overall inertial lift force on a particle in Pouiseille flow in a cylinder for a dilute suspension of particles; at low shear the equilibrium position is at 0.68 of the diameter corresponding roughly to the Segre-Silberberg position. At higher shear the equilibrium position moves nearer to the wall. From Matas and Morris (2004); reproduced with permission

Stokes flow which is time reversible for spherical objects meaning that viscous forces cannot operate (see, e.g. Cantat and Misbah 1999). Inertial-based lateral motion of a particle is therefore impossible. However, viscous lateral motion is possible and mainly relevant to deformable particles. The forces leading to lateral motion are described here. For further reading see Vlahovska et al. (2009).

- *Drag force*. Relative motion between the particle and the fluid will result in a drag force due to the viscous forces between the fluid and the particle surface.
- *Lift due to loss of particle symmetry*. An initially spherical particle which is deformable will become elongated as a result of the difference in drag on the particle from the wall and the non-wall side. In particular, the particle will have upstream–downstream asymmetry resulting in a viscous lift force (Olla 1997; Cantat and Misbah 1999).
- *Lift due to tank-treading*. A deformable particle undergoing tank-treading (see Sect. 3.3) near a wall will experience a lift force which causes it to move away from the wall (Olla 1997; Kaoui et al. 2008).

These forces contribute to the creation of a cell-free layer in the microcirculation where viscous flow dominates, discussed further in Chap. 8.

3.2.4 Chemical and Electrical Forces

These forces generally operate at close range and arise through interaction between particles, rather than through the dynamic behaviour of the fluid in which the particles are suspended. Figure 3.8 illustrates these two forces.

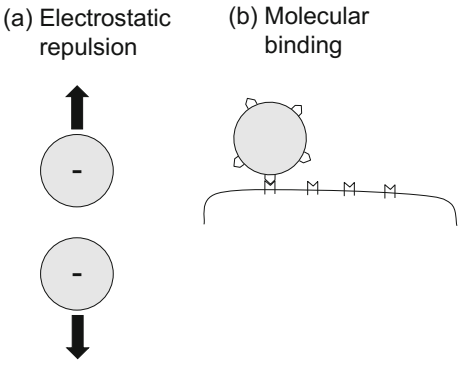

Fig. 3.8 Electrostatic and chemical forces on a particle in a fluid

- *Electrostatic forces*. Electrically charged particles will repel similarly charged particles and attract particles of opposite charge. Some particles may have overall neutral charge but the charge can be split in the form a dipole with a positive and negative end. In this case the positive and negative ends of adjacent particles attract and the similarly charged ends repel.
- *Molecular binding forces*. These concern the binding of one biological cell or molecule with another biological cell or molecule.

Electrostatic forces are important in that red cells, white cells and platelets all have a negative charge. This helps to keep them apart and helps prevent thrombus formation in the normal circulation. Electrostatic forces are also the origin of a lift force on deformable particles near a wall. If a particle deforms in shear flow near a wall, an electrostatic dipole will be produced which interacts with the mirror of the dipole in the wall producing a lift force (Leal 1980).

Molecular binding forces are especially relevant in blood flow and three phenomena will be considered in more detail; Rouleaux formation, leukocyte adhesion and platelet aggregation and adhesion.

Rouleaux formation Red cells at low shear clump together face to face to form rouleaux (Fig. 3.13). A review by Wagner et al. (2013) considers two explanations for this; the bridging model and the depletion model. Rouleaux formation in vivo is thought to require the presence of albumin and fibrinogen. If plasma is replaced with an isotonic saline solution then rouleaux formation does not take place. In the bridging model, albumin and fibrinogen are adsorbed onto the surface of the red cell. There is chemical bonding between the molecules on the surfaces of adjacent red cells, which is sufficient to overcome the electrostatic repulsion resulting in adhesion of red cells and rouleaux formation. In the depletion model, a randomly low concentration of albumin and fibrinogen concentration gives rise to a depletion force (see Sect. 3.2.5), which results in red cell adhesion and rouleaux formation.

Leukocyte adhesion Activated white cells travelling close to the vessel wall form molecular links with endothelial cells. These links are formed through bonding between ligands on the white cell and selectin molecules on the endothelium. If

other forces (e.g. related to particle inertia and shear) are greater than the molecular binding force then the link is broken, the white cell rolls along the endothelium until a link is re-established. This repeatedly happens and the white cell rolls along the endothelium until either the shear forces are sufficient to detach the white cell or the molecular links are strong enough to prevent the cell from rolling further. Leukocyte adhesion is a necessary step in the migration of leukocytes through the endothelium.

Platelet aggregation and adhesion Activated platelets chemically bond to each other via macromolecules (fibrinogen and von Willebrand factor) present in plasma. Platelets also adhere to collagen exposed by damaged endothelium. These are important steps in thrombus formation.

3.2.5 *Forces Arising from Collision*

Particles in a fluid are subject to collisions from both fluid molecules and other particles. These collisions give rise to a number of different forces (Fig. 3.9).

- *Fluid-particle forces (Brownian motion)*. Random variations in the number of fluid molecules impacting on the particle will produce small random forces which vary in magnitude and direction. This results in a particle suspended in the fluid having random erratic movements, called Brownian motion. This motion is more significant for particles with small mass, such as LDL cholesterol, and less so for heavier particles such as blood cells.

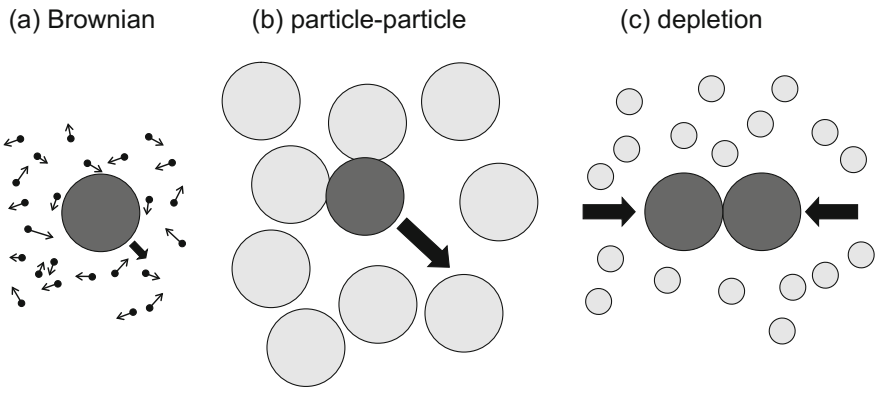

Fig. 3.9 Forces arising from collision of particles. **a** Forces arising from collisions from fluid molecules leading to a small force whose magnitude varies randomly in time and magnitude leading to small random movements of the particle (Brownian motion). **b** Forces arising from collisions between particles. **c** Depletion force. Where the large particles touch there is a region where small particles are excluded. This produces an attractive force between the two large particles

- *Particle–particle forces*. When the volume fraction of particles is small, collisions between particles are rare and the particles can be considered to be independent in that their main interaction is with the surrounding fluid and not with other particles. As the volume fraction increases collisions which are more common and becomes a major factor in determining the distribution of particles within the fluid volume and the viscous behaviour.
- *Depletion force*. If a fluid contains macromolecules such as albumin then these act to keep larger particles such as red cells apart. Where there is a local deficiency in macromolecules, occurring through random changes in their distribution, this will allow the larger particles to be in close contact. This is equivalent to a force and is called a 'depletion force' (Asakura and Oosawa 1958).

Whether the particle is solid or deformable is a key determinant of viscous behaviour. For a suspension of solid particles, the viscosity increases with volume fraction, linearly at first, but then non-linearly, finally reaching an infinite value at about 64 % volume fraction (Gondret 1997). At this concentration the fluid no longer flows as the particles cannot flow past each other due to the close proximity of their neighbours and the fluid behaves as a solid. For a suspension of deformable particles, the viscosity is lower than for a suspension of solid particles of the same volume fraction, and flow is maintained at higher volume fractions. It has been reported that a suspension of red cells will continue to flow for volume fractions up to 98 %. Figure 3.10 illustrates the viscosity—shear rate behaviour for idealised solid spheres and red cells.

In a suspension of identical particles, there is movement of particles across streamlines so that the particle distribution is non-homogeneous and consequently the

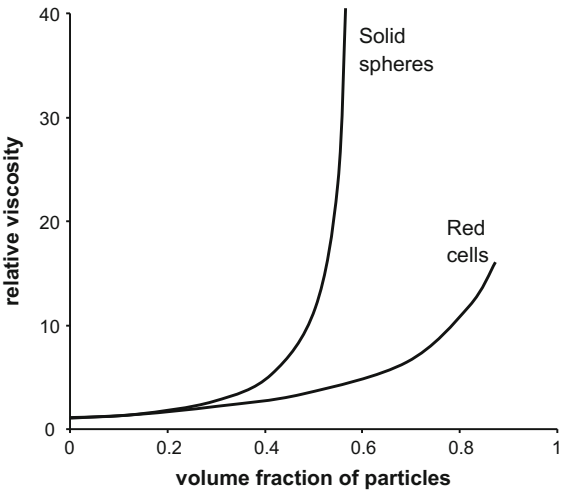

Fig. 3.10 Viscosity as a function of particle volume fraction for idealised solid particles and red cells at a shear rate of 200 s^{-1}. Red cell data from Goldsmith (1972). Solid particle data from Gondret (1997)

local viscosity is also non-homogeneous. The collision rate is dependent on the local shear gradient. A higher shear gradient means more particles flowing past each other, which results in more collisions. The collisions give rise to lateral displacement of the particles towards regions of lower collision rate and lower shear gradient. For steady flow in a tube, the shear gradient is zero at the centre of the tube increasing to a maximum at the wall. This can lead to higher particle concentrations at the tube centre than at the tube wall and blunting of the velocity profile (Lyon and Leal 1998; Kumar and Graham 2012a). This phenomenon is generally described with respect to low Reynolds number flows (<1), however in principle it is also applicable to higher Reynolds number flows including at physiological values seen in large arteries. For example, the study below by Aarts et al. (1988) reports decreased red cell concentration at the vessel walls in a 3 mm vessel with a Reynolds number of between 280 and 1150, which is comparable to that in arteries.

For flow of a suspension of particles of different size there are, in addition to the interactions described above, interactions between the different types of particles. The 1988 study by Aarts investigated the distribution of platelets and red cells in a suspension of red cells at 45 % haematocrit. This was undertaken in a glass tube of 3 mm diameter at wall shear rates from 240 to 1260 s^{-1}; comparable to physiological flow in a small artery such as the brachial or anterior tibial arteries. The platelets were suspended in a saline fluid and also in a suspension of red cell ghosts at 45 % volume fraction. Red cell ghosts are red cells rendered optically transparent by removal of their haemoglobin. During preparation, the red cells are made to burst spilling the haemoglobin contents. After washing and immersion in saline, the red cell membranes reform in a biconcave shape. Figure 3.11a shows the distribution of platelets when immersed in saline. There is accumulation roughly midway

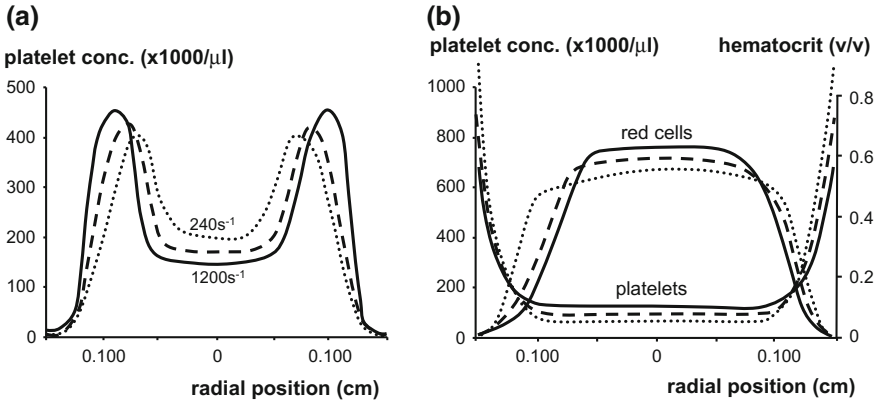

Fig. 3.11 Red cell and platelet distribution with radial position for blood flowing in a tube of 3 mm internal diameter. **a** Platelets in saline at wall shear rates of 1200 s^{-1} (*solid line*), 760 s^{-1} (*dashed line*), 240 s^{-1} (*dotted line*). **b** platelets in ghosts (optically transparent red cells); same wall shear rates as (**a**). From 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(6):819–824, reproduced with permission

between the wall and the centre of the tube, as expected from the Segre-Silberberg effect. When immersed in ghosts, the platelets mostly accumulate near the vessel wall (Fig. 3.11b). The phenomenon of cell accumulation near the vessel wall is called 'margination'. Blood cell margination has been studied using both experimental techniques and computational modelling (see reviews by Kumar and Graham 2012a, b). Cell stiffness rather than cell size is thought to be the principle determinant of cell margination. Platelets, white cells and diseased red cells arising from malaria and sickle cell disease are all stiffer than normal red cells and all marginate. The process of margination is further enhanced by rouleaux formation (Nash et al. 2008). Margination of stiff particles by red cells looks to be a design feature of the cardiovascular system. Platelets are pushed to the wall so that they can be available for endothelial repair and thrombus formation. White cells are pushed to the wall so that they can be available for combating infection in tissues by crossing the endothelium.

3.3 Viscous Behaviour of Blood

This section provides a discussion on the viscous behaviour of blood including variations in viscosity within the vessel. The viscous behaviour of blood is almost entirely dominated by the behaviour of red cells, so this section will focus on the behaviour of red cells with shear rate and vessel diameter, and their effect on white cells and platelets.

3.3.1 Behaviour of Single Blood Cells

A mammalian biological cell consists of a lipid bilayer (the cell membrane), intracellular fluid (cytoplasm) and a skeletal structure (cytoskeleton) which gives the cell rigidity and through which cell movement is effected, and various internal structures (organelles). The lipid bilayer is some 6 nm thick and acts like an incompressible 2D fluid in that the surface area is difficult to increase but the elements of the bilayer may flow over the surface of the cell. When a cell is subject to shear the bilayer may flow around the cell in the same way that the tracks of a tank rotate around the drive wheels (hence the term 'tank treading'). The cytoskeleton consists of filaments and tubules which are anchored at proteins floating within the lipid bilayer.

A number of methods exist for measuring the viscoelastic properties of cells and the reader is referred to the article by Yamada et al. (2000) for a review of some of these methods. Reported values of stiffness and viscosity for blood cells are provided by Tran-Son-Tay and Nash (2007). For the purpose of this chapter it is sufficient to note that platelets and white cells are much stiffer than red cells and this qualitative description will allow us to explore their behaviour in flow.

In the red cell, the cytoskeletal network ('spectrin') is immediately below the lipid bilayer and is coupled to it at various points. The spectrin network determines the biconcave shape of the red cell. Spectrin has shape-memory so after deformation the red cell reassumes its biconcave shape.

The biconcave disc shape allows the red cells to undergo considerable deformation without a change of surface area, and more importantly, without rupture of the cell. At low shear ($\sim 3\ s^{-1}$) the red cell will undergo tumbling but still maintains its biconcave shape. At slightly higher shear ($\sim 6\ s^{-1}$), the red cell will experience tank-treading (Dupire et al. 2012). As the shear rate increases, the red cell deforms, becoming stretched with the long axis aligned at an angle with respect to the flow. The degree of stretching increases with shear rate (Fig. 3.13). In small diameter tubes at low Reynolds numbers (comparable to flow in the microcirculation) the red cell deforms and a number of characteristic shapes are seen (Fig. 3.12). For diameters of 4–7 μm the red cell resembles a bullet; for diameters of 7–10 μm, where red cells travel in a single line, the cell resembles a parachute, for higher diameters the red cells interact and may assume a slipper shape. In the extreme case, the deformability of the red cell allows it to squeeze through an orifice of only 3 μm in diameter.

White cells are observed to take much longer than red cells in traversing capillaries and this is put down to the increased stiffness of white cells. White cells contribute significantly to resistance in microvascular beds. If there is increased white cell stiffness as a result of cell activation, or if there is decreased perfusion as a result of disease, then white cells can get stuck in the capillary bed with local occlusion of blood flow (Tran-Son-Tay and Nash 2007).

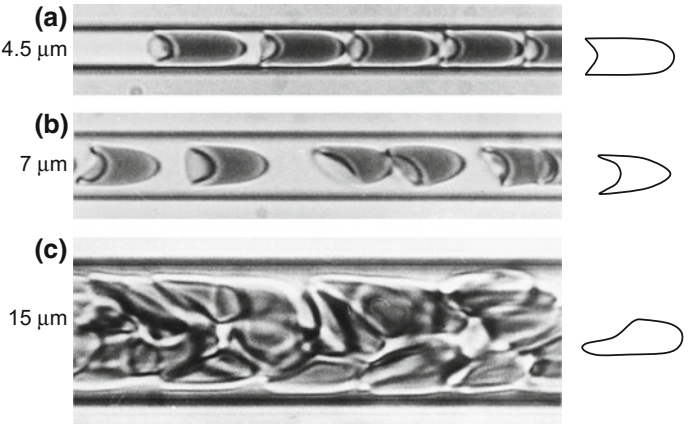

Fig. 3.12 Flow of blood in small diameter tubes; **a** 4.5 μm—the red cell distorts to a *bullet shape*, **b** 7 μm, the red cell distorts to a *parachute shape*, **c** 15 μm—some of the red cells have *slipper shapes*. Reprinted from Pries AR, Secomb TW. Blood flow in microvascular networks. In: Tuma RF, Duran WN, Ley K, editors. Handbook of Physiology: Microcirculation. pp. 3–36, Copyright (2008) with permission from Elsevier

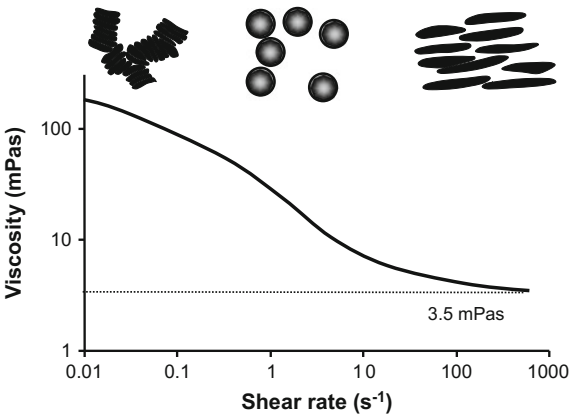

Fig. 3.13 Schematic of whole-blood viscosity as a function of shear rate and of the appearance of red cells at different shear rates. There is rouleaux formation at low shear; independent red cells at intermediate shear; elongation at high shear. The high-shear viscosity is 3.5 mPa s

3.3.2 Viscosity—Shear Rate Behaviour of Whole Blood

A cone plate viscometer is typically used to measure the change in viscosity of blood as a function of shear rate. Figure 3.13 shows that blood is a shear-thinning fluid in which the viscosity decreases with increasing shear rate. This behaviour can be explained entirely through changes in the red cell behaviour. In other words the viscous behaviour of whole blood is dominated by the red cell behaviour, not that of white cells or platelets.

At low shear, the high viscosity results from the presence of rouleaux. At very low shear, the rouleaux will form an interlocking structure which requires a small yield stress before flow occurs. As shear rate increases rouleaux formation decreases and viscosity decreases. At shear rates above about 10 s^{-1} rouleaux do not form. Red cell deformation occurs for a shear rate above about 1 s^{-1}. As shear rate increases, red cells elongate and partially align themselves with the flow direction causing decrease in viscosity. At the highest shear rates, there may be layering of red cells with plasma rich regions, which further decreases viscosity. Figure 3.14 is a schematic of the contribution of red cell aggregation and deformation to the viscous behaviour of blood with varying shear rate. If it is assumed that red cells are stiff then the viscosity is roughly constant with shear rate. Adding aggregation results in an increase in viscosity at low shear. Adding deformation results in a reduction in viscosity at higher shear. Further details on the effect of aggregation and deformation can be found in Chien (1970). Table 3.2 summarises the behaviour of red cells in whole blood at increasing shear rate.

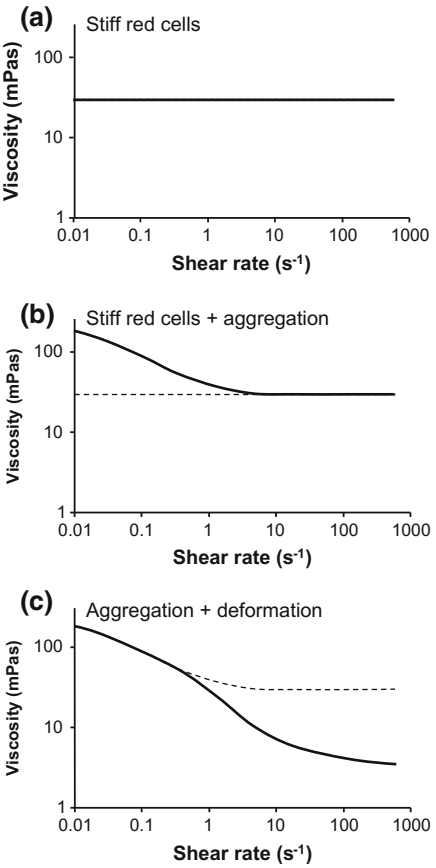

Fig. 3.14 Schematic of the contribution of various components to the viscosity of whole blood. **a** Viscosity for red cells which are stiff and independent. **b** Viscosity when red cell aggregation is included. **c** Viscosity when red cell deformation is included

Table 3.2 Summary of red cell behaviour at different shear rate

Shear rate (s^{-1})	Red cell behaviour
0–0.01	Virtually all red cells form rouleaux Rouleaux tangle forming an interlocking structure like a solid There is a very small yield stress
0.01–1	Rouleaux length decreases Chains align themselves with respect to flow direction
1–100	Very few rouleaux present; none above about 5 s^{-1} Red cells begin to deform, elongating and aligning with flow direction
100–1000	Red cells are elongated Red cells may form layers with plasma in between (which reduces viscosity)

3.3.3 *Viscosity—Diameter Behaviour of Whole Blood*

Two historical studies are commonly used to illustrate phenomena involving flow of blood in small diameter vessels; one by Fahraeus in 1929 and the other by Fahraeus and Lindqvist in 1931, and in each case the effects observed have been named after the authors (Fig. 3.15). The Fahraeus effect is that the haematocrit of blood in a tube of small diameter is less than the haematocrit of blood in the receiving tank. The effect is most pronounced at a tube diameter of 12–13 μm. The Fahraeus–Lindqvist effect is that the viscosity in the tube (measured from pressure and flow) depends on tube diameter, reaching a minimum viscosity at a tube diameter of 7 μm. The key feature is the presence of a layer near the wall which is free of red cells. Observations of a cell-free layer were made by Pouiseulle in the

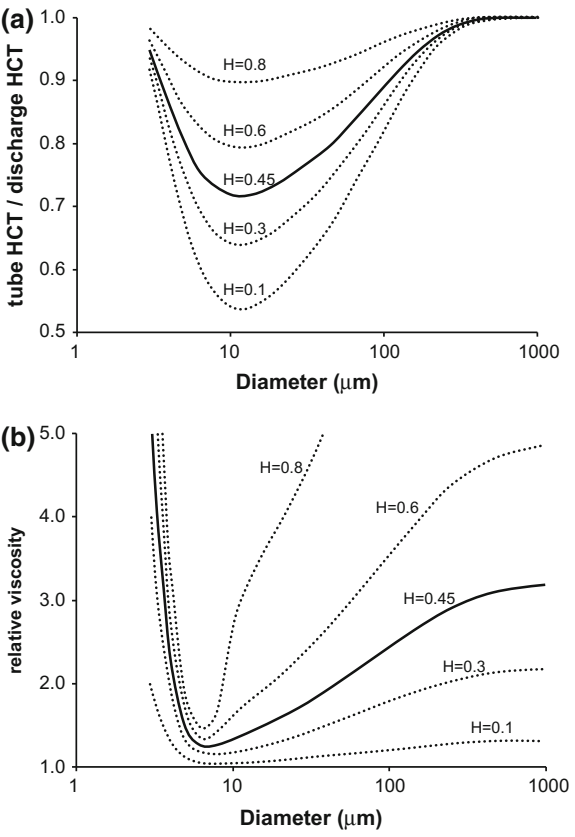

Fig. 3.15 Flow of blood in glass tubes at different haematocrit. **a** Fahraeus effect; the ratio of tube haematocrit (*H*) to discharge haematocrit is less than 1 and has a minimum value at 12–13 μm diameter. **b** Fahraeus–Lindqvist effect; the relative viscosity is dependent on diameter with a minimum value at 7 μm diameter. Best-fit equations were used taken from Pries et al. (1990, 1992)

mesenteric circulation of the frog in the nineteenth century. Fahraeus and Lindqvist hypothesised that the reduced viscosity in the plasma layer near the wall (1.8 mPa s as opposed to 3–4 mPa s for whole blood) meant that the effective viscosity for flow of whole blood was reduced. The presence of a cell-free layer also explains the Fahraeus effect. The plasma layer near the wall moves at low velocity and the red cells in the centre of the vessel move at high velocity. The overall result is that the relative volume of red cells to plasma is greater in the discharge fluid than for the fluid in the tube. Both these effects have been extensively investigated by others, extending the range of diameters and the range of haematocrit values. Figure 3.15 is based on best-fit equations to experimental data obtained by Pries et al. (1990, 1992). These effects are most relevant for the microcirculation where vessel diameter varies from 5 to 10 μm in capillaries to a maximum diameter of around 200 μm in arterioles.

We will now examine the origin of the plasma free layer seen in the Fahraeus and Fahraeus–Lindqvist effects. From Sect. 3.2 we have seen that there are several wall lift forces which could potentially give rise to a cell-free layer, and some of these are dependent on Reynolds number. For Fahraeus–Lindqvist experiments, Reynolds numbers may be calculated from the data provided by Pries et al. (Table 1, 1992). These show a range of *Re* values from 0.001 to 360 (Fig. 3.16). There are therefore several causes of the plasma-free layer seen for flow of blood in glass tubes. For low $Re < 1$, viscous effects will dominate and so viscous lift forces are relevant. For high $Re > 1$, inertial lift forces are relevant. Where the diameter is sufficient to allow several red cells adjacent to each other, there will be collisions and red cell migration towards the tube centre. For low diameters, only one red cell at a time can travel along the pipe and there is a lift force associated with asymmetry of the particle.

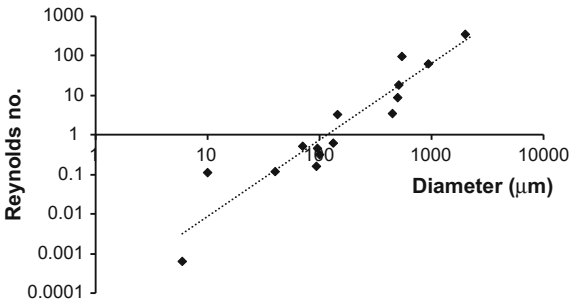

Fig. 3.16 Reynolds number versus tube diameter for experimental data exploring the Fahraeus–Lindqvist effect (calculated from data in Pries et al. 1990)

The themes explored in this section, axial accumulation of red cells, the presence of a cell-free layer, forces arising from deformation of particles, reduction of viscosity in small vessels and local variations in haematocrit are all relevant to the microcirculation and are explored further in Chap. 8.

3.3.4 Viscous Behaviour in Arteries

This section discusses viscous behaviour in vivo in the human arterial system. Table 3.3 summarises the main feature of viscous behaviour for the different cardiovascular system components, including arteries.

Arteries in the human have a diameter from 25 to 30 mm for the ascending aorta down to 1 mm for the smallest arteries. The heart acts to mix blood thoroughly so that the red cell distribution leaving the heart is homogeneous. Peak Reynolds numbers (*Re*) are below 2000 apart from the ascending aorta during ejection of blood where values of 4000–5000 regularly occur. Flow in healthy arteries is therefore laminar apart from a brief period immediately post-systole in the ascending aorta. One might expect that flow would be described by laminar streamlines and effects concerning lateral migration across streamlines should be considered. It was noted above that forces leading to lateral migration across streamlines are always present in suspensions of particles. The study by Aarts in a 3 mm vessel with physiological Reynolds number did show depletion of red cells near the wall. It is, however, generally thought that in arteries, red cells are uniformly distributed apart from a small cell-free region near the wall, which has no effect on overall viscosity. At the time of writing, there does seem to be a lack of

Table 3.3 Flow and red cell behaviour in the components of the cardiovascular system

Component	Peak Reynolds number	Turbulence?	Red cell aggregation?	Homogeneous distribution of red cells?
Heart	5000–20,000	Yes	No	Yes
Arteries	5000 (ascending aorta) 500 (smallest arteries)	In ascending aorta (post-systole)	No	Yes
Microcirculation	0.5 (largest arterioles) 0.0003 (capillaries)	No	Yes	No
Veins	100 (smallest veins) 3000–4000 (vena cavae)	No	Yes	No

definitive studies on which to base this conclusion. Most of the discussion above on force and effects has considered straight tubes and axial flow. In the arterial system, it is recognised that there is a strong helical flow component in most arteries so that flow is not axial. It has been shown that helical flow has a strong mixing effect (Caro et al. 2005; Cookson et al. 2009), though these studies were on spiral flow in grafts. It is possible that the helical flow in arteries acts to mix the red cells leading to a greater homogeneity than would be the case if there were no helical flow.

In Sect. 3.2.2, it was noted that the viscosity of whole blood in arteries is shear dependent reaching a plateau value for shear rates above about 200 s^{-1}. The measured mean shear rate in large arteries is 200–300 s^{-1} and the maximum shear is 800–1000 s^{-1} (Wu et al. 2004). The assumed homogeneous distribution of red cells and the high mean and maximum shear rates in arteries has led to the conclusion that most of the time it is reasonable to treat blood as a Newtonian fluid with a viscosity equal to that from the high-shear region, commonly taken as 3–4 mPa s (e.g. see Pedley 1980). Most of the theoretical, experimental and computational studies on blood flow have assumed that blood is a Newtonian fluid. However most large arteries, especially those supplying muscle, have periods of reverse flow where the mean velocity passes through zero, and some arteries have no flow for a period during diastole. In this case the wall shear rate will be much less than 200 s^{-1} and it is likely that non-Newtonian effects are present. Evidence for non-Newtonian behaviour in vivo comes from simulation studies performed using computational modelling. These investigate velocity profile and wall shear stress distributions using a Newtonian viscous model, and then using a non-Newtonian model. Figure 3.17 is taken from Johnston et al. (2004) showing wall shear stress in the coronary artery estimated using computational fluid dynamics using a Newtonian model and a Power law model of viscosity. There are clear differences in wall shear stress, especially at the low velocities of 0.02 m s^{-1}. Figure 3.18 shows velocity profiles in

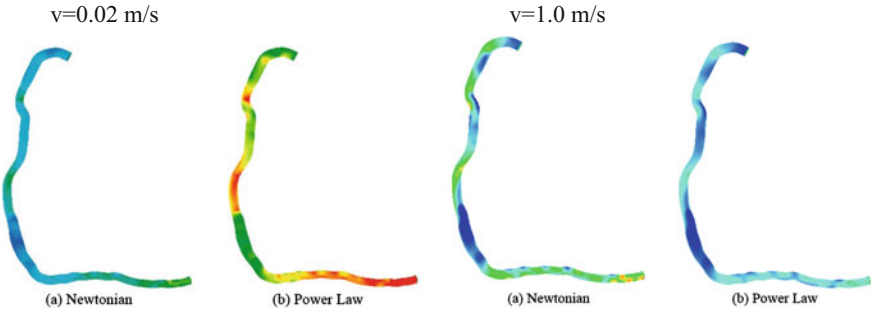

Fig. 3.17 Effect of non-Newtonian viscosity model on wall shear stress. Simulated flow was undertaken in a coronary artery with Newtonian and Power Law non-Newtonian viscous models. Differences are most pronounced at the lower velocity of 2 cm s^{-1}. Reprinted from Journal of Biomechanics Vol. 37, Non-Newtonian blood flow in human right coronary arteries: steady state simulations, Johnston BM, Johnston PR, Corney S, Kilpatrick D; pp. 709–720; Copyright (2004) with permission from Elsevier

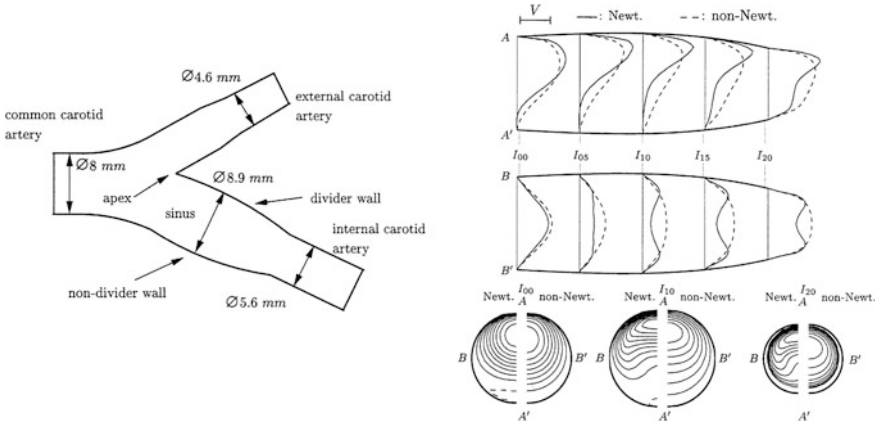

Fig. 3.18 Effect of non-Newtonian viscosity model on the bulk flow field. Simulated flow in the carotid bifurcation was undertaken using a Newtonian and non-Newtonian viscous model. There are differences in velocity profile and in iso-velocity contours. Reprinted from Journal of Biomechanics, Vol. 32, Gijsen FJH, van de Vosse FN, Janssen JD; The influence of the non-Newtonian properties of blood on the flow in large arteries: Steady flow in a carotid bifurcation model; pp. 601–608, Copyright (1999), with permission from Elsevier

an idealised bifurcation estimated using a Newtonian and a non-Newtonian model (Gijsen et al. 1999), again showing clear differences in the estimated flow field data. Non-Newtonian behaviour in arteries is therefore relevant to both the bulk flow field and wall shear stress. The non-Newtonian behaviour in arteries is due to red cell deformation, not aggregation. Ideally non-Newtonian behaviour should be taken into account in blood flow modelling studies, but mostly is not.

Diseased arteries are associated with reduction in local diameter for atherosclerotic plaque and increase in local diameter for an aneurysm. In both cases, there are regions where low shear rate may persist for substantial proportions of the cardiac cycle (Fig. 3.19). If there is a local vortex, then shear will be low and the conditions are suitable for red cell aggregation. There is also evidence from experimental flow studies (Shuib et al. 2011) and from computational modelling (Jung and Hassanein 2008) which suggest that there may be local reductions in red cell concentration (Fig. 3.20). These effects may be relevant in vivo and are the subject of research at the time of writing.

3.3.5 Viscous Behaviour in Other Parts of the Cardiovascular System

From a rheological point of view, the cardiovascular system may be divided into the heart, arteries, microcirculation and veins. Table 3.3 summarises the viscous

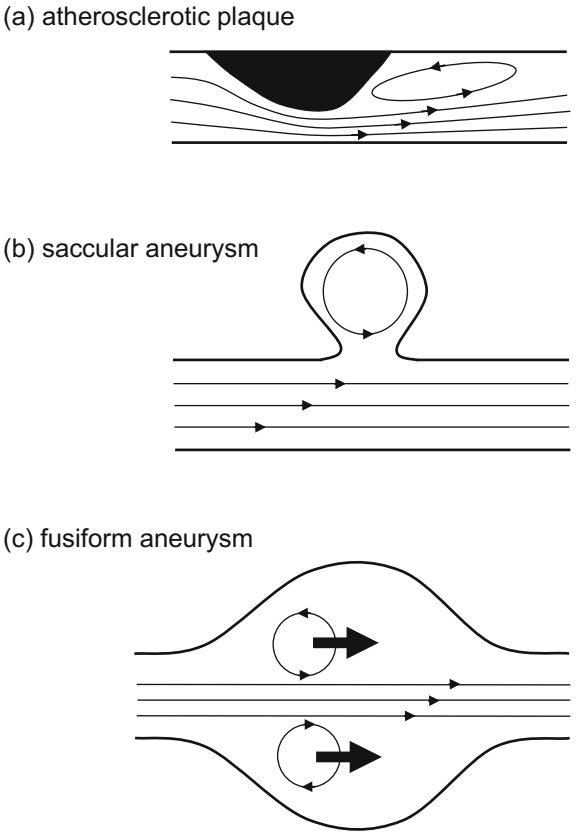

Fig. 3.19 Vortex production in arterial disease which is associated with low shear and can provide suitable conditions for red cell aggregation. **a** Atherosclerotic plaque—a vortex is present in the post-stenotic region which may be stable or which may be shed downstream. **b** Berry aneurysm—a stable vortex is present. **c** Fusilar aneurysm—a vortex ring may be generated which propagates downstream during the cardiac cycle

features of blood in these various compartments. The heart is associated with high Reynolds number flow involving considerable mixing and the treatment of blood as a homogeneous Newtonian fluid with a high-shear viscosity is usually reasonable. Flow in the veins is generally of low Reynolds number (<500), so flow is mostly laminar. In vivo evidence from ultrasound identifies the presence of rouleaux in venous flow (Cloutier et al. 1997; Wang and Shung 2001) suggesting that the

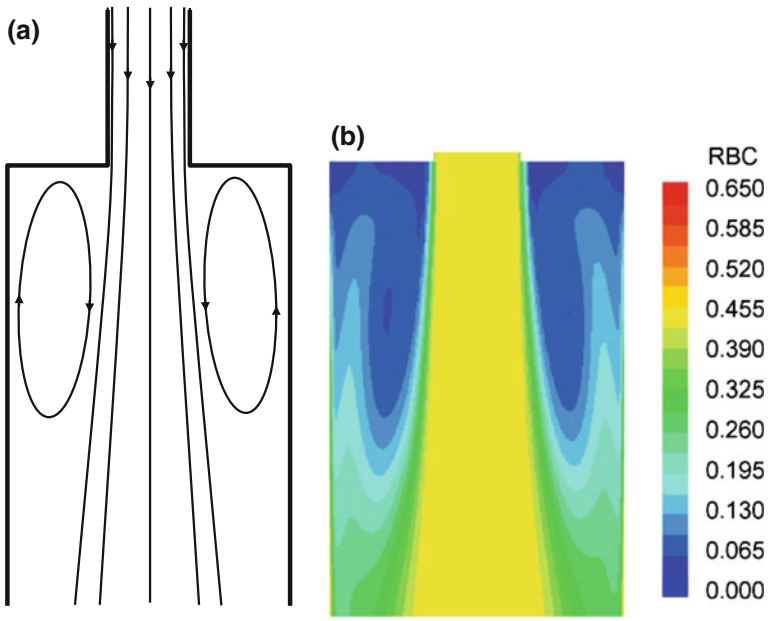

Fig. 3.20 Reduction in red cell volume fraction in low shear regions. Simulated flow of red cells was undertaken for an expansion with volume fraction of 45 % and a maximum velocity of 70 cm s^{-1} at the inlet. **a** Schematic of geometry and flow streamlines. Flow in the inlet has a maximum velocity in the centre of the tube. In the expansion regime there are stable vortices either side of the main flow. **b** Volume fraction of red cells. In the core this is 45 % however in the low shear side regions the volume fraction is as low as 5 %. This suggests that particles may not be distributed uniformly in the region downstream of stenoses in vivo. Reprinted from Medical Engineering and Physics, Vol. 30, Jung J, Hassanein A; Three-phase CFD analytical modeling of blood flow; pp. 91–103, Copyright (2008), with permission from Elsevier on behalf of IPEM

non-Newtonian properties of blood are important. Flow in the microcirculation is complex and covered in detail in Chap. 8, building on the discussions of the Fahraeus and Fahraeus–Lindqvist effects covered in Sect. 3.3.3.

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