PART ONE

ARTERIAL CIRCULATION

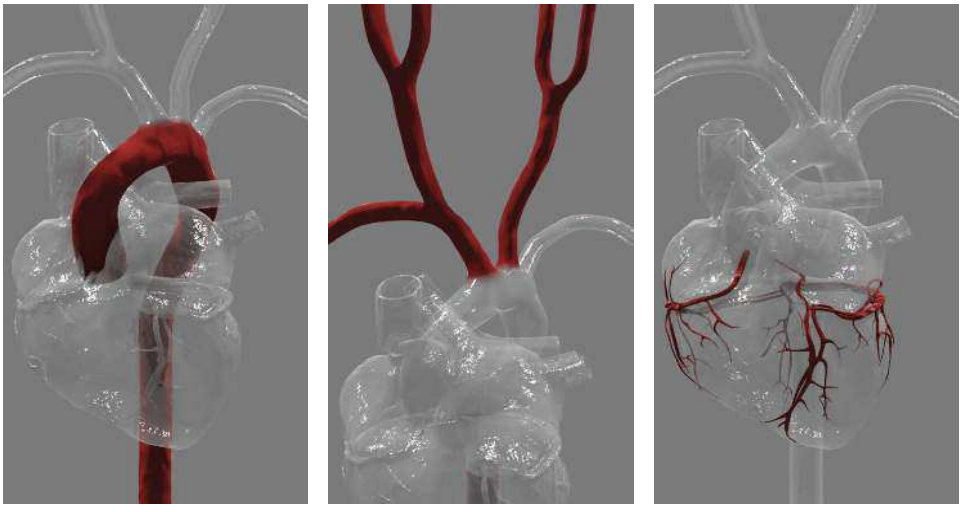
1

Basic facts about quantitative physiology

The cardiovascular system is a closed circuit that carries oxygenated blood to all the tissues and organs of the body. Functionally, it can be regarded as made up of three compartments: the *heart*, the *systemic* and *pulmonary circulations*, and the *microvasculature*. In this chapter we will recall the most important features of the physiology of the systemic circulation characterizing the mathematical models that will be introduced later on. We will also highlight the main peculiarities of the pulmonary circulation. Heart physiology will be addressed in Chapter 4.

The systemic circulation is made up of the arteries, which carry oxygenated blood ejected by the left part of the heart to the living tissues, and the veins, which allow non-oxygenated blood to return to the right part. The exchange of oxygen between blood and the body tissues occurs in the microvasculature, which in fact separates the systemic arterial tree from the venous systems. In the pulmonary circulation, non-oxygenated blood ejected by the right part of the heart flows in the pulmonary arteries towards the lungs where it becomes oxygenated and goes back to the left part through the pulmonary veins.

Blood is composed of *plasma* (about 55% of its total volume), which consists of water (about 92% of plasma volume), proteins and ions. The remainder corresponds to the blood cells, of which 97% of the volume is made up of *erythrocytes* (red blood cells), which carry the oxygen in oxygenated blood. The other cells are *leucocytes* (white blood cells) and *platelets*. The diameter of blood cells is approximately 10^{-3} cm, whereas that of the smallest arteries and veins is about 10^{-1} cm. This is why blood in the systemic and pulmonary circulations is often considered to be Newtonian, that is, characterized by a linear relationship between internal forces and velocity gradients (Perktold and Hilbert 1986, Formaggia *et al.* 2009*a*). However, in the smallest arteries, such as coronary arteries (the arteries perfusing the



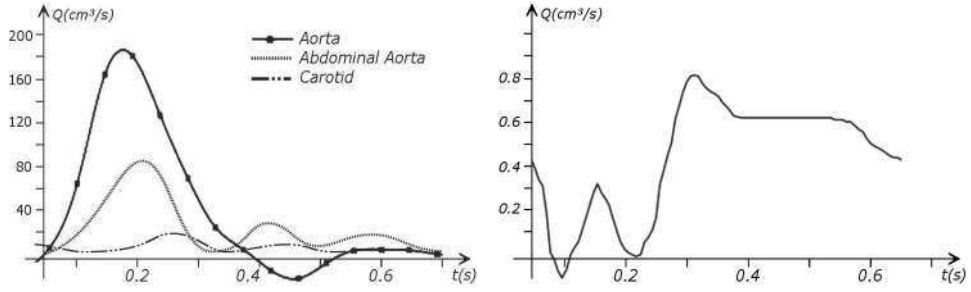
(a) (b) (c)

Figure 1.1 The aorta (a), the carotid arteries (b) and (a subset of) the coronary arteries (c).

heart and the corresponding veins; see Figure 1.1(c)), in the aortic root (where the blood flow reaches its peak velocity) or in the presence of vessel narrowing (stenosis), non-Newtonian blood rheology is more appropriate: see *e.g.* Chen, Lu and Wang (2006), Fasano and Sequeira (2017) and references therein.

Thanks to the synchronous heart contraction, blood flow is pulsatile, and blood is pumped into the two circulations by means of discrete pulses with a pressure usually varying during a heartbeat in the ranges 70–130 mmHg and 20–30 mmHg for the systemic and pulmonary networks, respectively (1 mmHg $\simeq 133.3$ Pa $= 1333$ g cm^{-1} s^{-2}).

In the systemic circulation, blood first enters the *aorta* (the largest artery with diameter equal to about 2.5 cm in adults: see Figure 1.1(a)) and then flows through a network of hundreds of branching arteries of decreasing size, reaching all the regions of the body. Dimensions and numbers of veins are comparable with those of arteries. The waveform of the flow rate as a function of time is characterized by different peak values when moving downstream towards the smallest arteries. In particular, the flow rate peak value is about 200 cm^3 s^{-1} in the aorta, 80 cm^3 s^{-1} in the abdominal aorta, 15 cm^3 s^{-1} in the carotid arteries (the arteries supplying blood to the brain: see Figure 1.1(b)), and 1 cm^3 s^{-1} in the coronary arteries (corresponding to a maximum blood velocity of about 150 cm s^{-1} in the aorta, 100 cm s^{-1}



(a) (b)

Figure 1.2 Typical flow rate waveforms in the ascending aorta, abdominal aorta and carotid arteries (a), and in the coronary arteries (b).

in the abdominal aorta, 80 cm s^{-1} in the carotid arteries and 40 cm s^{-1} in the coronary arteries). Further, the shape of the waveforms changes while moving downstream: see Figure 1.2(a). In particular, in the ascending aorta, after the systolic peak, the flow rate decelerates assuming null or even negative values, whereas in the abdominal aorta and in carotid arteries it is more spread out and always positive. In any case, we can distinguish the *systolic phase* – the interval of acceleration and deceleration of blood flow – and the *diastolic phase* – the interval of almost constant or possibly reverse flow.[1] A different situation occurs in coronary arteries, where the peak flow rate is reached during diastole: see Figure 1.2(b). The coronary arteries are not directly fed by the heart; indeed, blood in the proximal part of the aorta (the sinuses of Valsalva from which the coronary arteries originate) during diastole is allowed to enter the coronary arteries thanks to the elastic response of the aorta and isovolumic ventricle relaxation (see below for more details). The systemic circulation also comprises the venous system which returns the de-oxygenated blood to the right part of heart.

In the pulmonary circulation blood first enters the *pulmonary artery* (diameter equal to about 3.0 cm in adults) and then flows into another network of branching arteries of decreasing size reaching the lungs. The waveforms and peak intensities are similar to those of the systemic arteries. After oxygenation in the lungs, the blood returns to the left heart through the pulmonary veins.

The different characteristics of blood flow in the arteries of the systemic

[1] The above definition of systole and diastole is formulated from the perspective of the arteries. An almost equivalent definition could be given from the perspective of the heart and possibly for each of its chambers: see Chapter 4.

circulation result in different values of the *Reynolds number*,

$$Re = \frac{\rho_f \, D \, U}{\mu},$$

(where ρ_f is the blood density, D and U are the characteristic vessel dimension and blood velocity, respectively, and μ is the fluid viscosity), a dimensionless number which quantifies the importance of inertial forces over the viscous forces. In the cardiovascular system this variability is mainly due to the size of the vessel and blood velocity. In particular, $Re \simeq 4000$ in the aorta and $Re \simeq 400$ in coronary arteries, with intermediate values found when moving downstream along the aorta. Thus, blood covers a range of Reynolds numbers where both the inertial and the viscous components of the flow are relevant. Although in the aorta Re is higher than the critical value of 2000 above which the flow would no longer be laminar in a straight pipe, the pulsatile nature of blood flow does not allow transition to full turbulence in physiological conditions. It is debatable whether transition to turbulence effects occur in the aorta. Some authors speculate that the helicoidal velocity pattern in the aorta, induced by the torsion of the heart's contraction, inhibits any transition to turbulence, thus supporting the thesis that in healthy conditions fully developed turbulence is never observed in the cardiovascular system (Morbiducci *et al.* 2009). This is not necessarily the case for some pathological conditions, such as carotid stenosis, yielding a narrowing of the vessel lumen and increased complexity of the geometry together with higher Reynolds numbers: see *e.g.* Ahmed and Giddens (1984), Lee *et al.* (2008), Kefayati, Holdsworth and Poepping (2014) and Lancellotti *et al.* (2017). The *Womersley number*,

$$W = \sqrt{\frac{2 \, A \, f}{\mu}},$$

(where A and f are the characteristic cross-section vessel area and time frequency of the flow rate signal, respectively) is a dimensionless number quantifying the pulsatility of flow. We find decreasing values in the systemic circulation moving downstream: $W \simeq 10$ in the aorta, $W \simeq 3$ in the carotid arteries. Similar values of Re and W are found in the pulmonary arteries.

In the veins of the systemic circulation, we find values of the flow rate, Reynolds and Womersley numbers comparable to the arteries, the only difference being that the blood flow waveform is more spread out than for the corresponding arteries. Another major difference is given by blood pressure values. In the arteries the range of pressure is almost the same, independent of the location in the tree (70–130 mmHg), whereas in the veins it reduces,

assuming an average value of about 10 mmHg. This is due to the high resistance experienced by blood flow in the microvasculature. The latter is composed of thousands of *arterioles* and *venules* and billions of *capillaries*. The blood velocity and vessel dimensions are here greatly reduced (about 10^{-1} cm s^{-1} in the former and 10^{-2} cm in the latter). This means that *Re* is very small (typically much smaller than one) in comparison with the systemic circulation since viscous forces completely dominate the inertial forces. As a result, the highest resistance to flow is found in the microvasculature, thus provoking a big decrease in the blood pressure. Since the typical dimension of capillaries is comparable to that of erythrocytes, a multiphase (multicomponent) model seems appropriate for their mathematical description (Enden and Popel 1992). Finally, we observe that most veins are supplied with valves that prevent backflow of blood, and venous flow is highly sensitive to muscle contraction and respiratory effects.

As observed, blood pressure assumes the same range of values along the entire systemic arterial tree, 70–130 mmHg. More precisely, negligible dissipation is experienced by the pressure signal in large and medium sized vessels before reaching the small vessels and microvasculature. Of course, at a given instant the pressure is not constant in space along the tree. Indeed, a time shift characterizes the pressure waveforms at different locations which generate gradient pressures between proximal and distal regions facilitating blood movement. These spatial gradients are due to the propagating nature of the pressure, which is in fact a wave travelling along the arterial network. The pressure wave speed ranges from about 500 cm s^{-1} in the aorta to 1200 cm s^{-1} in the coronary arteries. The presence of bifurcations or high-resistance regions, such as the microvasculature, produces wave reflections that propagate back towards the heart.

The propagation of a pressure wave along the vascular tree is due to vessel *compliance*, that is, the ability of the vessel to distend under the forces exerted by blood pressure. Vessel wall displacements are quite large, reaching up to 10% of the lumen diameter. This is possible thanks to the structure of the vessel walls: their total thickness is about 10% of the lumen diameter and they are composed of three layers: the *intima*, the *media* and the *adventitia*. The inner part of the intima is the *endothelium* (facing the blood), whereas the remaining part is made up of connective tissue. The media and the adventitia play a major role in characterizing the mechanical response of the vessel wall. Their main structural components are *elastin* and *collagen*. The media is also formed of *smooth muscle cells* which provide tone to the vessel wall. Elastin forms complex networks that are very distensible, providing the elasticity of the vessel wall at small strain. In contrast, collagen

forms stiff fibres oriented in a helical form providing tensile strength at large strain; see *e.g.* Tricerri, Dede', Deparis, Quarteroni, Robertson and Sequeira (2015) and Tricerri, Dede', Gambaruto, Quarteroni and Sequeira (2016) for cerebral arteries. Thus, the artery vessel wall is characterized by highly nonlinear elastic properties. The quantity of elastin and collagen progressively decreases moving downstream along the arterial network, whereas the quantity of smooth muscle cells increases. This allows the proximal arteries (those close to the heart), in particular the aorta, to be very extensible and, thanks to the high peripheral resistances due to the elevated tone of the distal arteries and to the microvasculature, to store about 50% of the blood entering during systole. This blood reserve is then discharged during diastole owing to the vessel wall elastic response (the so-called *windkessel effect*). This effect is responsible for the smoothing of the blood flow waveform discussed above, going downstream along the arterial network, which guarantees nearly continuous peripheral blood flow and thus an almost continuous exchange of oxygen with the tissues. Further, pulmonary artery walls are extensible too (with muscular tone increasing downstream), even though their thickness is only about 1% of the lumen diameter.

As already observed, there is mutual exchange of energy between blood and extensible vessel walls: the latter accumulate elastic potential energy under the forces exerted by the blood pressure, which is then transferred to the blood as kinetic energy (from the mathematical point of view, this gives rise to the *fluid–structure interaction* problem). This process occurs at short time scales, proportional to the duration of a heartbeat (~ 1 s). Other interaction mechanisms may take place at larger time scales yielding wall modifications of vessel properties; these are usually referred to as growth and remodelling problems. This occurs in the case of several arterial diseases, such as *atherosclerosis* and *aneurysm* formation. In the first case, an increased permeability of vessel wall to lipoprotein provokes a cascade of events at the cellular level which leads to the accumulation of fatty material in the intima, just below the endothelium, and then to plaque formation in the media. Preferential sites of atherosclerotic plaque formation are the carotid arteries and the coronary arteries. The main complications are partial occlusion of the lumen with consequent (cerebral or cardiac) ischaemia, or even total occlusion resulting in (cerebral or cardiac) infarction. An aneurysm consists in the dilatation of the vessel wall with formation of a (possibly huge) bulge, mainly in the aorta and cerebral arteries, due to a loss of elastin and to the consequent remodelling of collagen, resulting in a weakening of the arterial wall; 80–90% of ruptured abdominal aortic aneurysms and 45% of ruptured cerebral aneurysms result in death. The role of blood

fluid dynamics has been recognized as crucial for the development of both of these diseases (Glagov, Zarins, Giddens and Ku 1988, Bagci *et al.* 2008). In particular, *wall shear stresses*, that is, the viscous/friction forces exerted by the blood on the endothelium, despite being 100 times smaller in magnitude than pressure, regulate the permeability of the wall to lipoprotein and determine the loss of elastin, thus playing an important role in atherosclerosis and aneurysm development. Other than the wall shear stresses, their spatial distribution and gradient play a major role. For both these arterial diseases, this supplementary interaction between fluid and structure occurs at time scales of several years.

More on the physiology of the systemic and pulmonary circulations and microvasculature in view of mathematical modelling is available in Nichols and O'Rourke (2005), Quarteroni, Tuveri and Veneziani (2000*c*) and Formaggia *et al.* (2009*a*), just to name a few.