Chapter 5
The Arterial System II. Forces, Adaptability and Mechanotransduction

Peter R. Hoskins

Learning outcomes

1. Describe the forces on the arterial wall and the typical magnitude of forces.
2. Describe Murray's law.
3. Discuss historical work on the variation of wall shear stress with arterial diameter.
4. Describe the Law of Laplace.
5. Describe the lamellar unit of structure in the arterial wall.
6. Describe arterial system design principles in terms of normalisation of stress; wall shear stress, longitudinal stress and circumferential stress.
7. Discuss the role of forces in growth and adaptability of arteries at different stages of life from embryogenesis to old age.
8. Define the term 'mechanotransduction'.
9. Discuss the 4 principles steps of mechanotransduction: mechanotransmission, mechanosensing, mechanosignalling and mechanoresponse.
10. Describe the effects of changes in wall shear stress on the endothelium.
11. Describe the decentralised model of endothelial mechanotransduction.
12. Describe potential endothelial mechanosensors.

This chapter is the second on arterial biomechanics and will explore the forces on arteries and their effect. The emphasis will be on normal function in this chapter. Arterial disease is considered in Chaps. 14–16. There are three main principles which underpin this chapter:

- The arterial wall is subject to forces which arise from blood flow and from blood pressure.
- The arterial wall is able to sense forces.

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- The arterial wall will alter its structure and geometry in an attempt to maintain these forces within a narrow range of values.

5.1 Introduction

5.1.1 Historical Introduction

This introduction will start by referencing a study performed by Thoma (1893). His study concerned the developing chick embryo and three observations were made concerning the relationship between forces and arteries which provide a useful indication of key ideas in the text below. These observations (quoted in Wagenseil et al. 2009) are:

- Vessel inner diameter (i.e. the luminal diameter) depends on blood flow.
- Vessel length depends on longitudinal forces exerted by surrounding tissues.
- Vessel wall thickness depends on blood pressure.

It will be seen below that it is wall shear stress (WSS) that determines mean vessel diameter, longitudinal stress that determines vessel length and circumferential stress that determines mean wall thickness.

5.1.2 Forces on Arteries

The arterial wall is subject to two forces from the blood; pressure and shear stress (Fig. 5.1). The blood pressure acts on the arterial wall and is balanced by circumferential stress (also called hoop stress) within the wall (Fig. 5.2). Typical

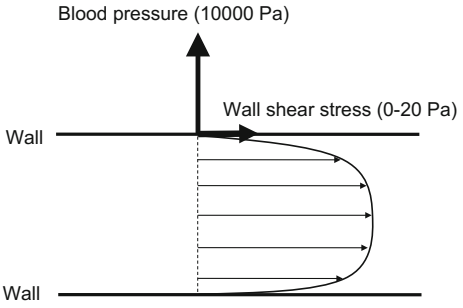

Fig. 5.1 Forces on an artery wall, blood pressure and wall shear stress

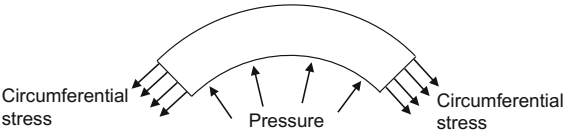

Fig. 5.2 Cross section of an artery wall. The pressure acts on the arterial wall. This is balanced by a circumferential stress within the wall

average values of these forces in the aorta are 90 mmHg (12,000 Pa) for pressure, 1 Pa for WSS and 12,000 Pa for circumferential stress.

The cyclic variation in pressure gives rise to a cyclic variation in the diameter and circumference of the artery. Each cell within the wall therefore undergoes a cyclic stretching and un-stretching. An artery diameter typically varies by 10 % over the cardiac cycle so each cell will typically be stretched and un-stretched by the same amount in the circumferential direction. The expansion in the circumferential direction is accompanied by a decrease in thickness in the radial direction. This can be seen as a cyclic variation in the thickness of the intima-media layer measured using ultrasound imaging (Meinders et al. 2003).

The WSS is the viscous drag of blood on the wall and acts in the plane of the wall. The WSS changes in a cyclic manner with changes in blood flow during the

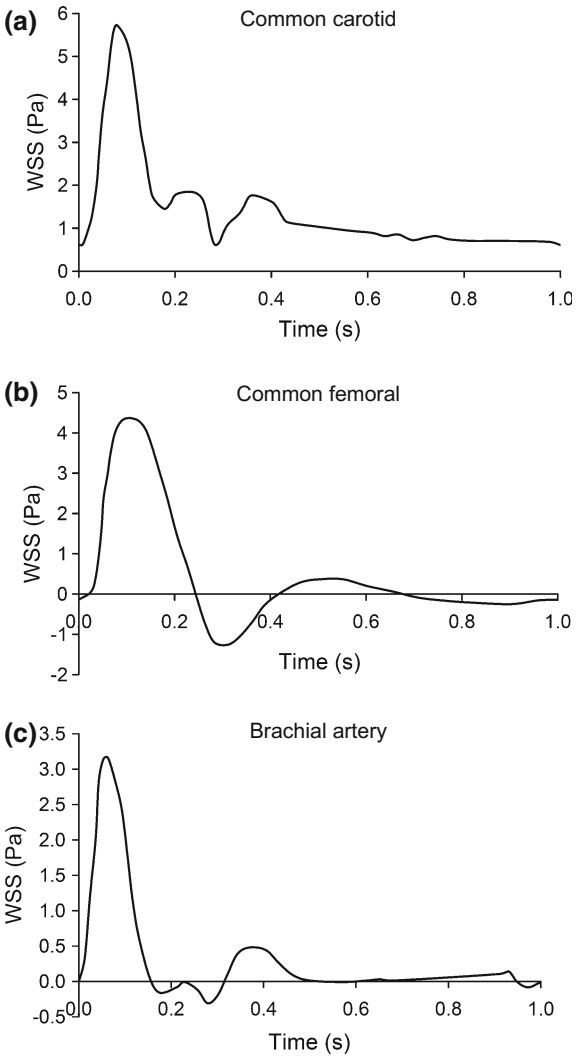

Fig. 5.3 Variation of WSS magnitude with time in the common carotid, common femoral and brachial arteries. Reprinted from Atherosclerosis, Vol. 191; Stroev PV, Hoskins PR, Easson WJ; Distribution of wall shear rate throughout the arterial tree: a case study; pp. 276–280, Copyright (2007), with permission from Elsevier

cardiac cycle (Fig. 5.3). If overall flow is axial then the WSS vector will also be axial. However in regions of complex flow such as near bifurcations the WSS vector may have a large non-axial component (Fig. 5.4).

If an artery is excised from the body its length will decrease by about 40 % implying that in vivo there is longitudinal tension; that is the artery is pre-stressed in the longitudinal direction (Fig. 5.5). If the excised artery is sliced open longitudinally it will partially spring open implying that the artery wall is also pre-stressed from the inner to the outer lumen. Arteries do not exist an unloaded state in vivo. In vivo, arteries are always in a longitudinally stretched state and are always subject to

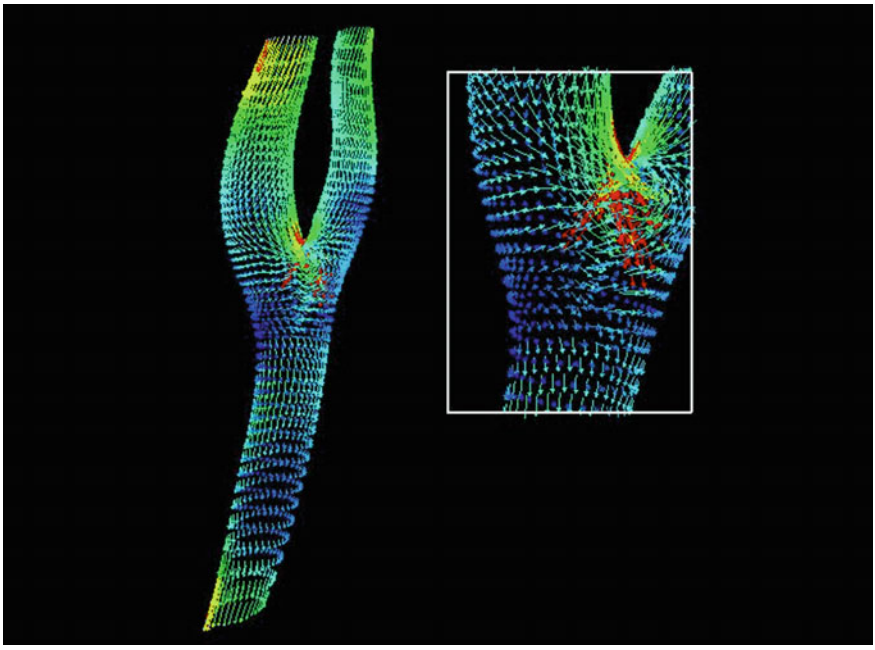

Fig. 5.4 WSS vector orientation in the carotid arteries at peak systole with large non-axial components close to the bifurcation. Image kindly provided by Prof Yun Xu, Imperial College

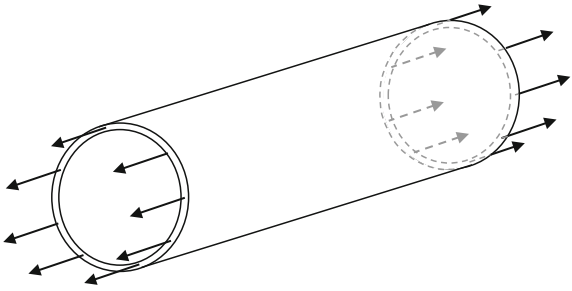

Fig. 5.5 Arteries in vivo are in a pre-stressed state in the longitudinal direction

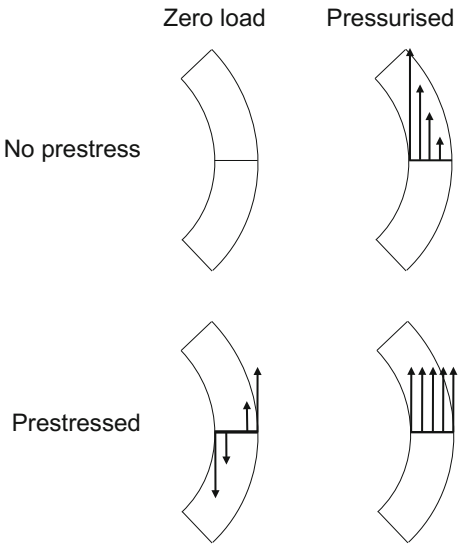

Fig. 5.6 Circumferential stress distribution in an artery with no blood pressure and with blood pressure, with and without pre-stressing. The stress distribution is uniform for the pressurised artery with pres-stressing

pressure. In the unloaded state this pre-stressing gives rise to an uneven stress distribution from inner to outer wall. However, in vivo under blood pressure, the stress distribution becomes more uniform (Fig. 5.6).

In the above analysis the artery is treated as a homogenous material. However, in reality, the presence of several layers (intima, media and adventitia) leads to a more complicated stress distribution due the different mechanical properties and the different amounts of pre-stressing in each layer (Holzapfel and Ogden 2010; Karsaj and Humphrey 2012).

5.1.3 Murray's Law

The arterial system is a branching network; the number of vessels increases with each branching and the diameters decrease. An early attempt to investigate the design of the branches was performed by Murray (1926a, b). He hypothesised that the arterial system is designed so that the heart needs to expend the minimum amount of effort in order to pump the blood along the arteries. From this he derived that the diameter d_1 of the parent artery to the third power is equal to the sum of the diameters d_2 and d_3 of the daughter arteries to the third power (Eq. 5.1, Fig. 5.7).

$$d_1^3 = d_2^3 + d_3^3 \tag{5.1}$$

This is known as Murray's law and has been widely quoted in publications on the structure of the arterial system. Though Murray did not concern himself with WSS it follows from Murray's law that the mean WSS is constant for all arteries

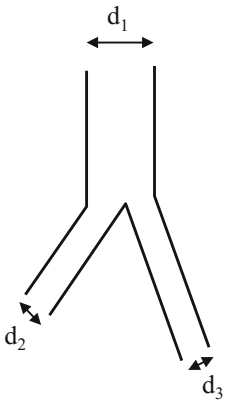

Fig. 5.7 Diameters of parent artery (d_1) and daughter arteries (d_2 and d_3) used in Eq. 5.1

from the largest to the smallest (Sherman 1981). It is also worth saying that if Murray's law applies to all mammals, which have basically the same design of cardiovascular system, then the WSS in all arteries in the whale should be the same, and the WSS in all arteries in the mouse should be the same.

The work of Murray is concerned with the principles by which the arterial system is designed. It follows that there must then be a mechanism for controlling arterial diameter according to some design principle. The mechanism suggested here is that the arterial system is designed to maintain WSS at a constant value (Zamir 1977). This is further considered below.

5.1.4 Brief Review of Wall Shear Stress

It was described in Sect. 5.1.3 that Murray's law predicts that the mean WSS is constant in all arteries. This section looks at experimental data on WSS and whether Murray's law has been confirmed to apply in vivo.

Early studies which estimated WSS in arteries assumed a parabolic velocity profile in the vessel. With this assumption an equation can be derived which relates wall shear rate to the flow rate and the diameter. In invasive studies flow rate can be measured using a variety of techniques including electromagnetic flow probes and thermodilution. Diameter can be measured using X-ray imaging or from calliper measurements in exposed vessels. These measurements need not even be made at the same time. Once the wall shear rate is calculated it is multiplied by viscosity to give the WSS. An early summary of WSS data is provided by Giddens et al. (1993) which demonstrated that mean WSS lies within the narrow range of 1–2 Pa in a range of arteries in the human and dog. This finding of a constant mean WSS is consistent with Murray's law and seemed to provide good confirmation that Murray's law was correct.

It is worth restating the situation in the early 1990s concerning WSS; Murray's law suggested that WSS is constant within a species; experimental findings suggested that WSS was similar in several different arteries in the human in the dog.

The constancy of WSS was challenged by later studies which used in vivo techniques based on MRI and ultrasound. The spatial resolution and functionality of in vivo imaging gradually improved to the point where it was possible to obtain reliable measurements of WSS in vivo. Advances in computing power and the availability of computational fluid dynamics also meant that by the 1990s it was possible to estimate WSS in realistic geometries (rather than in simple straight tubes). This combination of imaging and modelling data came up with a slightly different story concerning WSS which is summarised by Cheng et al. (2007). Figure 5.8 illustrates findings in 3 arteries, the common carotid, brachial and femoral. There are clear differences, with the common carotid having a higher mean WSS than the brachial or femoral arteries. It was also found that there are differences in WSS between species with smaller species having high WSS. An MRI study by Greve et al. (2006) demonstrated a dependence of mean WSS on body-mass to the power of −0.38, which is in excellent agreement with the dependence of −0.375 predicted by Weinberg and Ethier (2007) from scaling laws.

The evidence above points to a control mechanism which attempts to maintain WSS within a narrow bound (Langille 1996). The 'set point' for WSS in human arteries is around 1–2 Pa and deviation from this value will result in change in diameter; this is called 'arterial remodelling'. If the mean WSS is greater than the set-point, the diameter increases to reduce WSS until its value lies at the set-point. Conversely if the mean WSS is less than the set-point the diameter decreases until the mean WSS value lies at the set-point. It is noted that temporary increases in

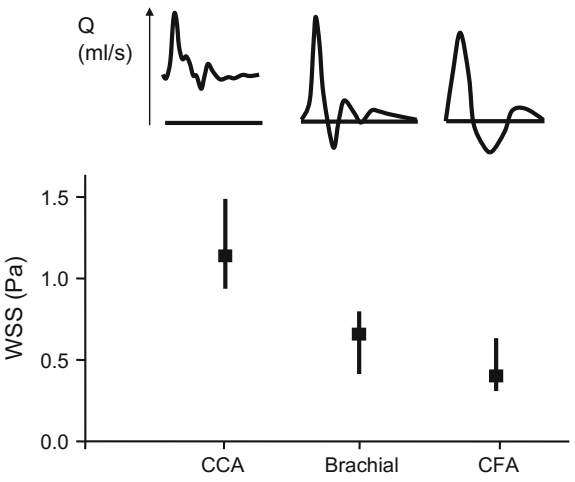

Fig. 5.8 Variation of mean WSS in the common carotid, femoral and brachial arteries. The differences are due to differences in the pulsatility of the flow waveform, with higher values of mean WSS for the carotid and lower values for the femoral and brachial. Data from Cheng et al. (2007)

mean WSS, such as occur during a few minutes exercise, will not result in long-term change in diameter. The control mechanism comes into play when the changes are longer term.

The discussion around Murray's law above suggests that it was initially thought that the value of the set-point for WSS was the same in all arteries. It has become clear that the set-point is different for different arteries. One possible explanation for this was offered by Reneman et al. (2006). He noted that the flow waveform is not the same in all arteries. This is illustrated in Fig. 5.8; the common carotid has a high degree of flow throughout the cardiac cycle (and higher mean WSS) whereas the brachial and femoral (which supply blood to muscle) have high pulsatility (and low-mean WSS). However during exercise the flow waveforms in arteries supplying muscle change significantly; the waveforms have a much higher component of flow and a much higher mean WSS. Reneman's observation was that *during exercise* the mean WSS is similar in different arteries, implying that the set-point may be relevant for conditions of high flow, not resting flow (for which most measurements are taken).

5.1.5 The Law of Laplace

It was noted above that blood pressure is opposed by a tension within the arterial wall. The relationship between pressure and tension was investigated by the French physicist Pierre de Laplace in the eighteenth century in the context of surface tension in water. Approximating an artery as a thin-walled cylinder gives the 'law of Laplace' as shown in Eq. 5.2.

$$T = P \cdot r \tag{5.2}$$

This states that, for a fixed pressure P, as the radius r increases the tension T in the wall increases. An alternative formulation of the law of Laplace is in the context of stress (force per unit area). The circumferential stress or hoop stress H is shown in Eq. 5.3 where w is wall thickness.

$$H = \frac{Pr}{w} \tag{5.3}$$

Figure 5.9 shows wall stress as a function of age in the aorta and carotid artery (from Åstrand et al. 2005). Values range from 3000 to 16,000 Pa.

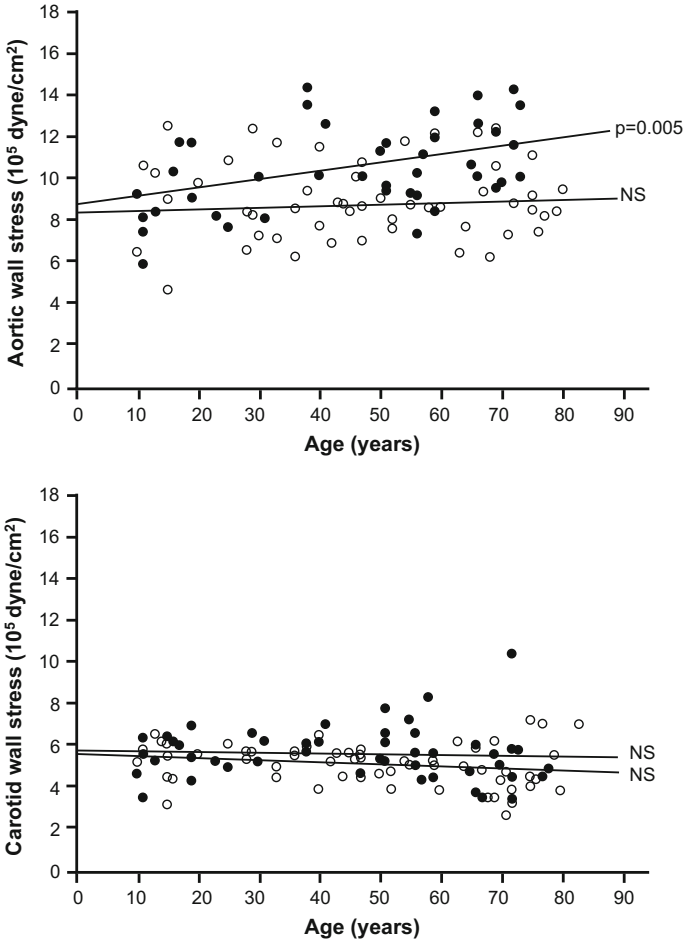

Fig. 5.9 Plots of circumferential stress as a function of age in the aorta and common carotid arteries. *Closed circles* are made, *open circles* female. Reprinted from Journal of Vascular Surgery, Vol. 42; Åstrand H, Rydén-Ahlgren A, Sandgren T, Länne T; Age-related increase in wall stress of the human abdominal aorta: an in vivo study; pp. 926–931, Copyright (2005), with permission from The Society for Vascular Surgery

5.1.6 *Brief Review of Circumferential and Longitudinal Wall Stress*

The mechanical strength of an artery is governed primarily by the elastin and collagen fibres which are laid down in a concentric fashion. The idea of a lamellar unit of structure consisting of muscle, elastin and collagen was formulated by Wolinsky and Glagov (1967). During fetal development the number of lamellar units increases and remains constant after birth. The number of lamellar units in the

adult aorta of different species was studied by Wolinsky and Glagov (1967). In decreasing order of animal size there are around 70 units in the pig, 60 in the human, 45 in the dog, 13 in the guinea pig and 5 in the mouse. The circumferential tension in the wall of the aorta increases with animal size (5 N m^{-1} for the mouse increasing to 190 N m^{-1} for the pig). However the significant finding reported in the Wolinsky paper was that the tension per lamellar unit was similar across all species at 1–3 N m^{-1}. Wall thickness therefore adjusts in order to maintain circumferential stress within a narrow range. Thickening of the wall during embryonic development occurs by increase in the number of lamellar units. Post-birth increases in wall thickness arise through thickening of each lamellar unit. In healthy individuals this is achieved by an increase in smooth muscle content, however in disease such as in hypertension thickening is accompanied by increasing collagen deposition and the changes become irreversible (Hayashi and Naiki 2009). Conversely, where there is decrease in circumferential stress, possibly as a result of disease, this leads to atrophy of the wall (Bomberger et al. 1980).

It was noted above that arteries are pre-stretched; that is there is longitudinal wall stress. Arteries are surrounded by a fibrous adventitia which is attached to tissues surrounding the other organs of the body. These organs will exert forces on the arteries via the adventitia which can be referred to as 'tethering forces'. The main determinant of structure within the body is the skeleton. As the skeleton grows the arteries will be subject to stretching which will increase the longitudinal stress. The response of the artery is to lengthen in order to normalise the longitudinal stress. However, where an artery is decreased in length it does not shorten to normalise the longitudinal stress and the result is a tortuous artery (Wagenseil and Mecham 2009).

5.2 Arterial System Growth and Adaptability

This section examines the role of forces in the growth and remodelling of arteries from the embryo through birth into old age. It is noted that there are gaps in the evidence base and the literature comes from several different mammals including chick, sheep and human. Further detail is provided in review articles (Langille 1996; Pries et al. 2005; Humphrey 2008; Hayashi and Naiki 2009; Wagenseil and Mecham 2009). This section is mostly not concerned with disease. The underpinning process governing growth and remodelling is termed 'mechanotransduction' and is described in detail in Sects. 5.3 and 5.4.

5.2.1 Embryogenesis

Following fertilisation of the mother's egg with the father's sperm the offspring begins to develop. The process starts with a single cell which quickly subdivides into many cells. During the initial few weeks of this development the offspring is

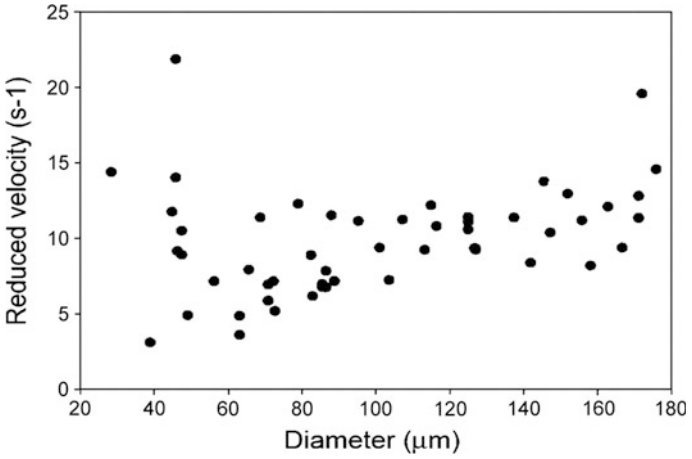

Fig. 5.10 Reduced-velocity (a measure of wall shear stress) versus diameter in embryonic arteries of the chick. Reduced-velocity is constant for arteries from 60–160 microns indicating the presence of a control mechanism. From; le Noble F, Fleury V, Pries A, Corvol P, Eichmann A, Reneman RS; Control of arterial branching morphogenesis in embryogenesis: go with the flow; Cardiovasc Res. 2005;65(3);619–28; by permission of the European Society of Cardiology

called an 'embryo' and the formation of the embryo is called 'embryogenesis'. Over time, a few days and weeks, organs form and a vascular system is laid down. The initial laying down of the vascular system, though fascinating, does not concern us. However once the earliest vessels are formed then these grow and develop into the vascular system; arteries, veins, capillaries etc. These immature simple vessels consist of a tube of endothelial cells without any surrounding smooth muscle, very similar to capillaries. The rudimentary heart pumps blood along the early vascular system and as the flow rate increases the arteries increase in diameter. Studies on the chick embryo (le Noble et al. 2005) estimated 'reduced-velocity' which is the ratio of blood velocity to diameter, as an index which was easy to calculate and proportional to WSS. They showed that reduced-velocity was similar for embryonic arteries greater than 40 μm in diameter (Fig. 5.10).

Even at this extremely early stage in the development of the arterial system 2 things emerge. First the constancy of reduced-velocity with diameter suggests a control mechanism in which diameter is adjusted to maintain reduced-velocity (i.e. shear stress) within a narrow bound; secondly that the endothelium (in the absence of any other cell types) is responsible for this control.

5.2.2 Fetal Growth

By the end of 8 weeks most of the major organs in the human embryo are in place and the remaining 32 weeks in the womb are spent growing. The embryo is now referred to as a fetus. Over this period the fetus grows from 3 g to 3 kg in weight,

and the arterial system also grows. The diameter of the aortic root (where the aorta emerges from the left ventricle) is 1 mm at 11 weeks increasing linearly with time to 9 mm at 40 weeks (Cartier et al. 1987; Achiron et al. 1998; Haak et al. 2002). There is very little literature on WSS in the fetus. Struijk et al. (2005) used ultrasound imaging in the descending aorta in fetuses with gestational age from 18 to 39 weeks, demonstrating that there was no change in mean WSS which had an average value of 2.2 Pa.

During the period from 8 weeks to birth the development of the arterial system can be described as follows; as the fetus grows, the cardiac output increases and the blood pressure increases. The arteries will increase in diameter in an attempt to maintain WSS at a constant value. The increase in pressure will result in an increase in wall thickness in an attempt to maintain circumferential stress at a constant value. This increase in thickness is associated with an increase in the number of lamellar units. The general enlargement of the skeleton and organs gives rise to an increase in longitudinal stress and the arteries will lengthen in an attempt to maintain longitudinal stress at a constant value.

5.2.3 Birth

The fetus is supplied with oxygen from the mother via the placenta and the umbilical cord. The left and right sides of the heart are connected via a hole (the foramen ovale) between the left and right atria, and the pulmonary and systemic circulations are connected via a bridging vessel (the ductus arteriosis) which links the pulmonary artery and the aorta. After birth the umbilical supply is cut and there are a number of plumbing changes which occur. The foramen ovale closes separating the left and right sides of the heart and there is closure of the ductus arteriosis separating the pulmonary and systemic circulations. The loss of the umbilical supply leads to an increase in pressure in the aorta and the reduction in pulmonary resistance leads to a decrease in pressure in the pulmonary artery. Before birth the aorta and pulmonary artery carry similar flow rate, have similar diameter and similar wall thickness. After birth the flow rate and diameter remain similar. However, there is increase in wall thickness of the aorta and decrease in wall thickness in the pulmonary artery. These changes in wall thickness are consistent with the renormalisation of circumferential stress following changes in pressure immediately following birth (Leung et al. 1977).

5.2.4 Childhood

Human life post-birth may be divided into two phases; birth to adulthood (childhood) at around 20 years when height no longer increases, then 20 years to death at age up to around 100 years.

In childhood the arterial system dimensions increase along with the dimensions of the rest of the body. Cardiac output increases and flow in each artery increases. There is an absence of literature in this area in childhood so what follows is conjecture based on the control theory described above. It is likely that the increase in arterial diameter is driven by the need to maintain WSS constant. The increase in pressure and diameter of arteries leads to increase in wall thickness. This is associated with an increase in the thickness of each lamellar unit, noting that the number of units in each artery is fixed at birth. Growth of the skeleton and organs leads to stretching of the arteries, and in response to the increase in longitudinal stress these elongate in an attempt to maintain longitudinal stress at a constant value.

5.2.5 *Adulthood*

During the second phase of ageing, from 20 years to death the arterial system does not remain of fixed dimensions. The aorta in particular increases in diameter. Figure 5.11a shows the diameter of the abdominal aorta as a function of age. From age 25 to 70 years the diameter increases by 20–25 % (Sonesson et al. 1993). As the adult is no longer growing the increase in diameter is not driven by increase in flow rate. The relevant fact is that the aorta increases in stiffness with age (Fig. 5.11b).

In Chap. 4 it was explained that ejected blood from the heart passes into the aorta, which is elastic and increases in diameter during the cardiac cycle in order to accommodate the blood ejected from the heart. If the aorta is stiffer then the diameter expands by a smaller amount. This in turn gives rise to increased blood velocity and increased WSS. Over time the aorta increases in diameter in an attempt to normalise WSS. Increase in blood pressure, arising through ageing and disease leads to increase

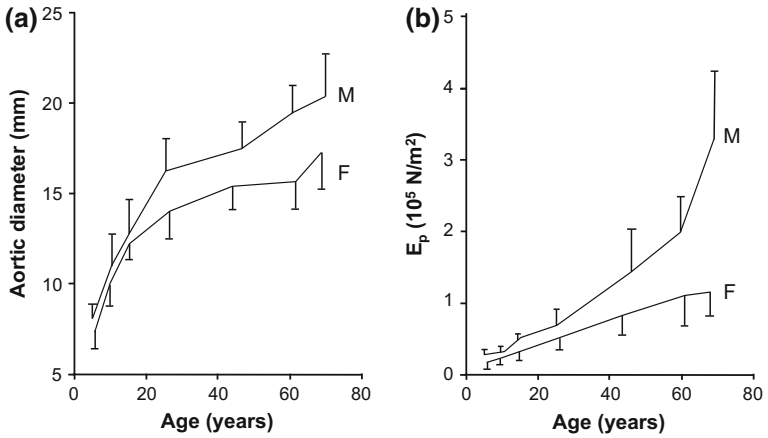

Fig. 5.11 Aorta diameter and stiffness as a function of age in the human. Reprinted from European Journal of Vascular Surgery, Vol. (7); Sonesson B, Hansen F, Stale H, Lanne T; Compliance and diameter in the human abdominal aorta - the influence of age and sex; pp. 690–697, Copyright (1993), with permission from Elsevier

in wall thickness. Chapter 14 discusses, in more detail, stiffening of arteries with ageing where it is noted that there are two principal mechanisms; loss of elastin due to cyclic stress fracturing and pathological changes associated with disease.

After age 40 there is loss in height mainly due to thinning of the intervertebral discs. Typically 1 cm is lost each decade with a total loss of up to around 10 cm. There will be shrinkage of associated arteries such as the aorta. In principle this could lead to tortuosity as noted above. Whilst age-related increased arterial tortuosity has been reported in regions subject to significant flexure (close to the knee, for example) (Wensing 1995) it is thought that increases in arterial tortuosity is mainly associated with a genetic defect which also leads to hyperflexible skin and hypermobility of joints.

5.2.6 *Intervention and Disease*

If mean flow rate is increased on a long-term basis then arterial diameter will gradually increase, reaching a maximum value at around 1–2 months. The change in diameter is called 'remodelling'. This is observed, for example in the human when dialysis fistulae are created. This involves direct connection of an artery and a vein in the arm in order to create a high-flow region from which blood can be drawn for passage through a dialysis system. The diameter of the radial artery increases during the post-operative maturing process which typically takes 6 weeks (Girerd et al. 1996). Similar changes occur in animals when fistulae are created (Masuda et al. 1999; Sho et al. 2004). Conversely, a decrease in flow rate over the long term will lead to reduction in diameter of the artery. For example in paraplegia there is severe muscle wasting and reduced blood flow in major arteries followed by reduction of arterial diameter (Reneman et al. 2006).

5.2.7 *Summary of the Control of Arterial Structure*

The key concepts which have been described above are summarised in this section. Figure 5.12 shows the three forces and their effect on the artery. These are

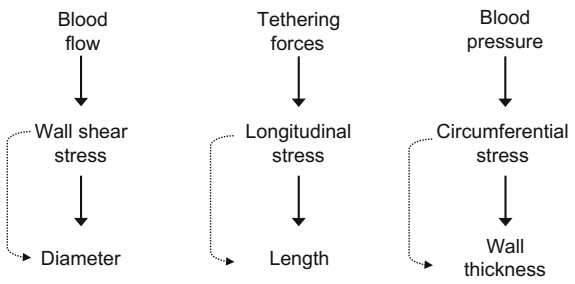

Fig. 5.12 The main control mechanisms relating to arterial structure

- *Arterial diameter and wall shear stress*. Long-term change in flow rate leads to change in WSS. The response of the artery is to change the diameter in order to renormalise WSS to a value around 1–2 Pa (though this value is different in different parts of the arterial system). Increase in WSS leads to increase in diameter. Conversely a decrease in WSS leads to decrease in diameter.
- *Arterial length and longitudinal stress*. Arteries are pre-stressed in the longitudinal direction, that is, there is a baseline longitudinal stress. Increase in tethering forces, which occur for example during growth, will lead to increase in longitudinal stress. The response of the artery is to lengthen to normalise the longitudinal stress. This mechanism only operates during growth. Decreases in tethering forces do not lead to shrinkage in the length of the artery; instead the artery will lengthen. This can lead to a tortuous geometry in experiments on animals, but tortuosity in humans is mainly thought to be associated with genetic defects.
- *Wall thickness and circumferential stress*. Long-term changes in blood pressure lead to changes in wall thickness in order to normalise circumferential stress. The response differs pre-birth and post-birth. Pre-birth wall thickness increases through an increase in the number of lamellar units. Post-birth the number of lamellar units is fixed and wall thickness increases by increase in the thickness of each unit. Initially wall thickening is associated with increased smooth muscle content. Post-birth, decrease in circumferential stress will lead to a decrease in wall thickness, and *vice versa*. In disease, for example hypertension, thickening is also accompanied by an increase in collagen which is irreversible.

Figure 5.12 shows these control mechanisms operating independently. In terms of developing a basic understanding of arterial biomechanics this assumption is sufficient. However, as noted by Pries et al. (2005), there is a level of interdependence.

5.3 Principles of Mechanotransduction

Virtually every cell in the human body is aware of its mechanical environment to some degree and will respond to changes in the mechanical environment. Mechanotransduction is the process whereby mechanical forces are translated into biological behaviour and vice versa. Mechanotransduction can be divided into four steps

- *Mechanotransmission*. A force is transmitted to mechanosensitive elements within the cell.
- *Mechanosensing*. The mechanosensitive elements detect the transmitted force.
- *Mechanosignalling*. The detected force results in events which are transmitted elsewhere in the cell.
- *Mechanoresponse*. A biological change is effected as a result of the detected signal.

This section explores general principles of mechanotransduction including each of the four steps listed above. This area is the subject of considerable research at the time of writing and the details of many of the steps below remain unresolved. The reader may wish to explore reviews of this area (Orr et al. 2006; Hoffman et al. 2011; Schwartz 2009).

5.3.1 Mechanotransmission

Cells are subject to external forces which result in stretching and displacement of the cell membrane and of its internal constituents. Some cells in contact with fluid, such as endothelial cells, are subject to shear stress on the surface of the cell adjacent to the moving fluid. These forces are transmitted to the mechanosensitive apparatus. In the case of endothelial cells, where mechanosensors are located on the cell surface, the force is applied directly to the mechanosensors (this is discussed further in Sect. 5.4). Force transmission through the cell is effected by the cytoskeleton. This intracellular structure is composed of filaments and microtubules which are stiff over a time period of microseconds and are capable of transmitting force from one part of the cell to another.

5.3.2 Mechanosensing

Within cells specialised units (mechanosensors) exist which are capable of detecting changes in their mechanical environment. If activated, mechanosensors can signal to other parts of the cell that there has been a change in the mechanical environment. The underlying physical basis for much of mechanosensing is the change in protein shape arising from force applied to the protein (Orr et al. 2006). Proteins are complex molecules which will adopt a shape ('conformation') corresponding to the lowest free energy. If a physical force is applied to one part of the protein then the shape will change in order to accommodate the applied force. In energy terms the protein moves to a different energy state. There are several types of protein conformation changes relevant to mechantransduction (Ingber 2006). These are:

- *Stretch-sensitive ion channel.* This is the most widely studied mechanosensor. Increase in the pressure within the cell during osmotic swelling will result in increase in tension in the lipid bilayer which opens allowing ions to either leave the cell or enter the cell (Sukharev et al. 2001) (Fig. 5.13). Alternatively tensional forces are transmitted direct from the cytoskeleton resulting in channel opening.

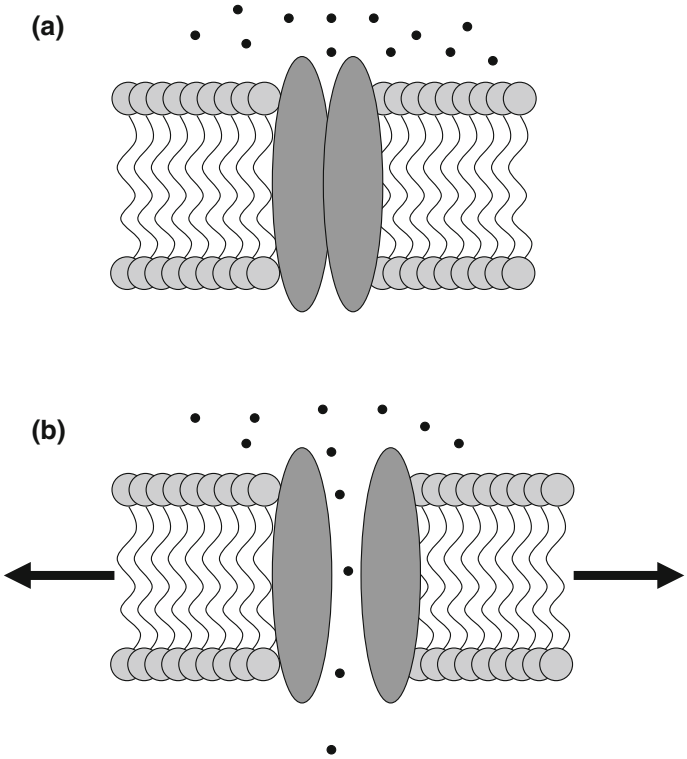

Fig. 5.13 Stretch sensitive ion channel. Increase in tension within the lipid membrane, arising from increase in pressure within the cell, leads to opening of the ion channel allowing passage of molecules in or out of the cell

- *Tension dependent distortion of an enzyme.* In the un-stretched state the enzyme acts to cleave the molecule it binds to. When a force is applied the enzyme is stretched and is unable to cleave the molecule.
- *Binding site exposure.* In the un-stretched state a binding site is hidden within the protein. Application of a force changes the shape of the protein revealing the binding site, in this example by stretching of the protein. The binding site is then available to bind local molecules.

5.3.3 Mechanosignalling

Mechanosensing is followed by triggering of events, the mechanoresponse. If the mechanosensors and the mechanoresponse occur in separate parts of the cell then the signal must be transmitted between the sensor and the area where the response

can be affected. Mechanisms for signal transmission are referred to as 'mechanosignalling' and there are two main mechanisms. The first is force transmission via the cytoskeleton, the second is release of chemicals which then diffuse through the cell. Mechanosignalling via the cytoskeleton is fast, with typical response times of a few hundred milliseconds. Chemical signalling is much slower with response times of the order of 10 s of seconds (Na et al. 2008).

5.3.4 Mechanoresponse

The mechanical response may be immediate as in the case of ion channels. More commonly the response involves pathways within the cell involving the nucleus of the cell and also signalling to other cells. In which case, the time-course of events can be days to months. Examples include bone deposition under increased weight bearing, or thickening of the arterial wall under a sustained increased blood pressure.

5.3.5 Switch-Like and Dynamic Models of Mechantransduction

The description of mechanotransduction above involves the detection of a force as an on/off process. The relevant protein involved in the mechanosensors changes conformation and the signal and subsequent response is either produced fully or not at all. However, in endothelial cells the response to WSS and to cyclic stretch depends on the frequency and to the detailed time variation, which an on/off model is unable to explain (Hoffman et al. 2011). Hoffmann et al. proposed a model of mechanosensing in which the time variation of the stimulus was accounted for.

5.3.6 Other Mechanosensory Mechanisms

It was noted above that protein conformation change is the dominant mechanism for mechanosensing. Another mechanism is compression of the intercellular space. Forces leading to reduction in the distance between cells will lead to changes in the concentrations of molecules in the gap between cells leading to increased binding at receptors on the cell surface; e.g. autocrine molecules in heart muscle (Maly et al. 2004).

5.4 Endothelial Mechanotransduction

It was noted above that the artery is subject to cyclic pressure which leads to a cyclic circumferential tension and cyclic stretch of all the layers of the artery (endothelium, media and adventitia), and the endothelium is subject to WSS. Of these elements by far the most important in terms of mechanotransduction is the effect of WSS on the endothelium. Most of the discussion below will be in terms of the combination of WSS and endothelium. Reviews of this area are provided by Ando and Yamamoto (2009), Davies (1995, 2009), Chien (2007) and Hahn and Schwartz (2009).

5.4.1 Effect of Wall Shear Stress on Endothelium

Laboratory studies of the effect of flow on arteries have largely concentrated on cultured endothelium; that is endothelial cells which are grown on a glass plate or similar material. Flow is then passed over the endothelium and a range of tests can be performed to investigate cell shape, orientation and the biological behaviour of the cells. Chapter 14 discusses cultured endothelium in more detail. Change in shear stress leads to a wide variety of effects as listed in Table 5.1. These have different timescales from potassium channel activation (seconds) to cell alignment (hours). Figure 5.14 shows cultured bovine endothelial cells before and several hours after a wall shear stress of 10 dyn cm^{-2}.

Table 5.1 Responses to changes in WSS in cultured endothelium (modified from Davies 1995); glycocalyx significance from Zeng and Tarbell (2014)

Timescale	Response	Significance
Secs	K+ channel activation	Related to vasorelaxation
Secs	NO release	Flow-mediated vasorelaxation
15–40 s	Ca^{2+} rise	Ca^{2+} as second messenger
2 min	PGI release	Regulation of vascular tone
Secs–mins	Remodelling of focal adhesion sites	Transmission/transduction stress
Mins–hours	Remodelling of the glycocalyx	Changes in mechantransduction, selective permeability and leukocyte adhesion
2–3 h	Induction protein kinase C	Regulation protein phosphorylation
>6 h	Cell alignment and direction change	Minimises the drag on cells

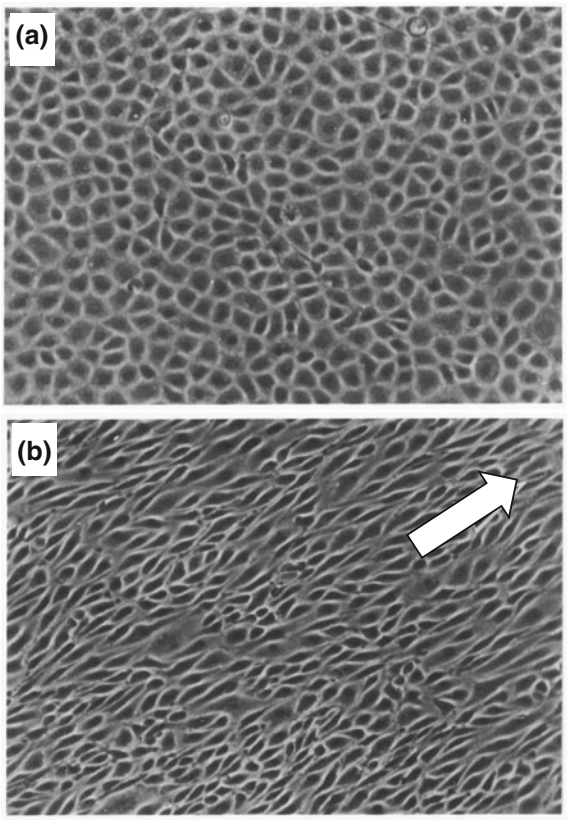

Fig. 5.14 Effect of wall shear stress on endothelial cell alignment using cultured bovine cells. **a** No wall shear stress; cells have a cobblestone appearance with no preferred direction, **b** several hours after wall shear stress of magnitude 10 dyn cm^{-2}; cells are aligned with the direction of wall shear stress. Images kindly provided by Prof. Peter Davies, University of Pennsylvania, USA

5.4.2 Decentralised Model of Endothelial Mechanotransduction

Mechanosensors can be divided between those on the endothelial surface adjacent to flowing blood and those embedded within the endothelial cell. It is thought that mechanosensors are distributed throughout the endothelial cell rather than just being on the surface. This is called the 'decentralised model of mechanotransduction' (Davies 1995; Helmke and Davies 2002). Figure 5.15 illustrates the main components involved in endothelial mechanotransduction in the decentralised model. In the figure, potential mechanosensors are located at four locations; (1) on the endothelial surface adjacent to flowing blood, (2) at the junction between cells, (3) at adhesion sites and (4) at the nucleus. Transmission of force between sites is effected by the cytoskeleton such that multiple locations may become activated near-simultaneously.

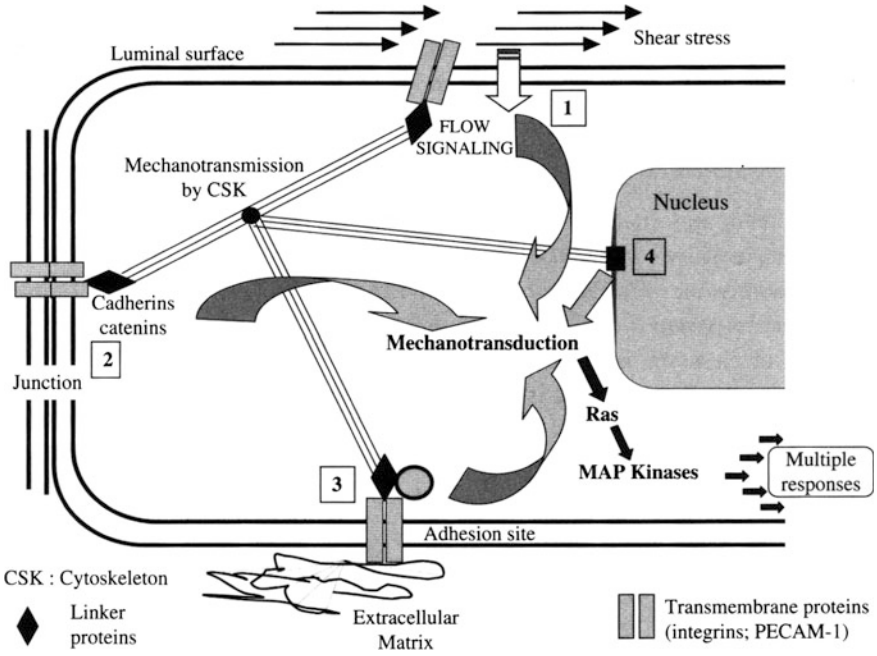

Fig. 5.15 Decentralised model of endothelial mechanotransduction. Reprinted by permission from Macmillan Publishers Ltd.: Nature Clinical Practice in Cardiovascular Medicine, Davies (2009), copyright (2008)

5.4.3 Potential Wall Shear Stress Mechanosensors

This section will describe mechanosensors. This is a highly active research area and understanding of the role of these sensors is continuing to evolve.

Luminal mechanosensors. Figure 5.16 illustrates mechanosensors present on the surface of the endothelium. These include ion channels (ATP, potassium and calcium), protein receptors (tyrosine kinase and G-coupled protein) and larger structures (glycocalyx and primary cilia). The shear force from blood flowing close to the endothelium will pull on the luminal proteins and luminal structures causing these to bend or change conformation. Potassium (K^+) and calcium (Ca^{2+}) ion channels are known to open in response to increased wall shear stress. Influx of calcium ions through open ion channels travels through the cell like a wave. The primary cilium extends several microns from the surface of the cell where shear force will be higher. The glycocalyx is a layer of glycoproteins which covers the surface of the endothelial cell projecting up to 4.5 microns.

Cytoskeleton. It has been proposed (Ingber 1997) that the cytoskeleton itself is constructed to stabilise the shape of the cell and to be able to detect changes in shape. The tensegrity model is one in which a matrix of stiff elements are held in a

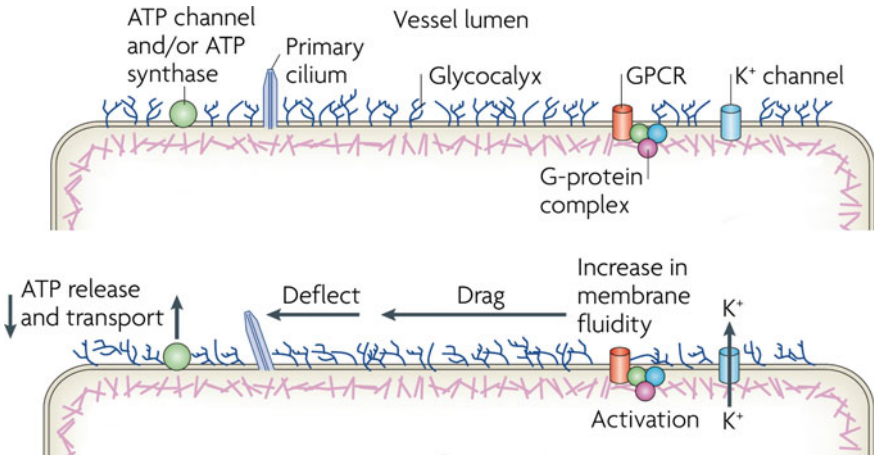

Fig. 5.16 Luminal mechanosensors. Figure adapted by permission from Macmillan Publishers Ltd: Nature Reviews of Molecular and Cellular Biology, Hahn C, Schwartz MA; Mechanotransduction in vascular physiology and atherogenesis, Vol. 10, pp. 53–62, copyright (2009)

stable configuration by the tension in elastic elements. Changes in shear will alter the tension distribution within the cell which is sensed by mechanosensors (adhesion proteins) connected to the cytoskeleton.

Adhesion proteins. The cytoskeleton is attached to proteins in the membrane referred to as 'adhesion proteins'. These adhesion proteins are subject to stress transmitted by the cytoskeleton and respond to this stress.

References

Achiron R, Golan-Porat N, Gabbay U, Rotstein Z, Heggesh J, Mashiach S, Lipit S. In utero ultrasonographic measurements of fetal aortic and pulmonary artery diameters during the first half of gestation. Ultrasound Obstet Gynecol. 1998;11:180–4.

Ando J, Yamamoto K. Vascular mechanobiology—endothelial cell responses to fluid shear stress. Circ J. 2009;73:1983–92.

Åstrand H, Rydén-Ahlgren A, Sandgren T, Länne T. Age-related increase in wall stress of the human abdominal aorta: an in vivo study. J Vasc Surg. 2005;42:926–31.

Bomberger RA, Zarins CK, Taylor KE, Glagov S. Effect of hypotension on atherogenesis and aortic wall composition. J Surg Res. 1980;28:402–9.

Cartier MS, Davidoff A, Warneke LA, Hirsh MP, Bannon S, Sutton MS, Doubilet PM. The normal diameter of the fetal aorta and pulmonary-artery—echocardiographic evaluation in utero. Am J Roentgenol. 1987;149:1003–7.

Cheng C, Helderman F, Tempel D, Segers D, Hierck B, Poelmann R, et al. Large variations in absolute wall shear stress levels within one species and between species. Atherosclerosis. 2007;195:225–34.

Chien S. Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell. Am J Physiol Heart Circ Physiol. 2007;292:H1209–24.

Davies PF. Flow-mediated endothelial mechanotransduction. Physiol Rev. 1995;75:519–60.
Davies PF. Hemodynamic shear stress and the endothelium in cardiovascular pathophysiology. Nature Clin Prac Cardiovasc Med. 2009;6:16–26.
Giddens DP, Zarins CK, Glagov S. The role of fluid mechanics in the localization and detection of atherosclerosis. J Biomech Eng. 1993;115:588–94.
Girerd X, London G, Boutouyrie P, Mourad JJ, Safar M, Laurent S. Remodeling of the radial artery in response to a chronic increase in shear stress. Hypertension. 1996;27:799–803.
Greve JM, Les AS, Tang BT, Draney Blomme MT, Wilson NM, Dalman RL, Pelc NJ, Taylor CA. Allometric scaling of wall shear stress from mice to humans: quantification using cine phase-contrast MRI and computational fluid dynamics. Am J Physiol Heart Circ Physiol. 2006;291:H1700–08.
Haak MC, Twisk JWR, Van Vugt JMG. How successful is fetal echocardiographic examination in the first trimester of pregnancy? Ultrasound Obstet Gynecol. 2002;20: 9–13.
Hahn C, Schwartz MA. Mechanotransduction in vascular physiology and atherogenesis. Nat Rev Mol Cell Biol. 2009;10:53–62.
Hayashi K, Naiki T. Adaptation and remodeling of vascular wall; biomechanical response to hypertension. J Mech Behav Biomed Mater. 2009;2:3–19.
Helmke BP, Davies PF. The cytoskeleton under external fluid mechanical forces: hemodynamic forces acting on the endothelium. Ann Biomed Eng. 2002;30:284–96.
Hoffman BD, Grashoff C, Schwartz MA. Dynamic molecular processes mediate cellular mechantransduction. Nature. 2011;475:316–23.
Holzapfel GA, Ogden RW. Modelling the layer-specific three-dimensional residual stresses in arteries, with an application to the human aorta. J Royal Soc Int. 2010;7:787–99.
Humphrey JD. Vascular adaptation and mechanical homeostasis at tissue, cellular, and sub-cellular levels. Cell Biochem Biophys. 2008;50:53–78.
Ingber DE. Tensegrity: the architectural basis of cellular mechanotransduction. Annu Rev Physiol. 1997;59:575–99.
Ingber DE. Cellular mechanotransduction: putting all the pieces together again. FASEB J. 2006;20:811–27.
Karsaj I, Humphrey JD. A multilayered wall model of arterial growth and remodelling. Mech Mater. 2012;44:110–9.
Langille BL. Arterial remodeling: relation to hemodynamics. Can J Physiol Pharmacol. 1996;74:834–41.
le Noble F, Fleury V, Pries A, Corvol P, Eichmann A, Reneman RS. Control of arterial branching morphogenesis in embryogenesis: go with the flow. Cardiovasc Res. 2005;65:619–28.
Leung DY, Glagov S, Mathews MB. Elastin and collagen accumulation in rabbit ascending aorta and pulmonary trunk during postnatal growth. Correlation of cellular synthetic response with medial tension. Circ Res. 1977;41:316–23.
Maly IV, Lee RT, Lauffenburger DA. A model for mechanotransduction in cardiac muscle: effects of extracellular matrix deformation on autocrine signaling. Ann Biomed Eng. 2004;32:1319–35.
Masuda H, Zhuang YJ, Singh TM, Kawamura K, Murakami M, Zarins CK, et al. Adaptive remodeling of internal elastic lamina and endothelial lining during flow-induced arterial enlargement. Arterioscl Thromb Vasc Biol. 1999;19:2298–307.
Meinders JM, Kornet L, Hoeks APG. Assessment of spatial inhomogeneities in intima media thickness along an arterial segment using its dynamic behaviour. Am J Physiol Heart Circ Physiol. 2003;285:H384–91.
Murray CD: The physiological principle of minimum work. I. The vascular system and the cost of blood volume. Proc Natl Acad Sci USA. 1926a;12:207–214.
Murray CD. The physiological principle of minimal work applied to the angle of branching of arteries. J Gen Physiol. 1926;9:835–41.
Na S, Collin O, Chowdhury F, Tay B, Ouyang M, Wang Y, Wang N. Rapid signal transduction in living cells is a unique feature of mechanotransduction. Proc Natl Acad Sci USA. 2008;105:6626–31.

Orr AW, Helmke BP, Blackman BR, Schwartz MA. Mechanisms of mechanotransduction. Dev Cell. 2006;10:11–20.
Pries AR, Reglin B, Secomb TW. Remodeling of blood vessels: responses of diameter and wall thickness to hemodynamic and metabolic stimuli. Hypertension. 2005;46:726–31.
Reneman RS, Arts T, Hoeks APG. Wall shear stress—an important determinant of endothelial cell function and structure—in the arterial system in vivo. J Vasc Res. 2006;43:251–69.
Schwartz MA. The force is with us. Science. 2009;323:588–9.
Sherman TF. On connecting large vessels to small the meaning of Murray's law. J Gen Physiol. 1981;78:431–53.
Sho E, Nanjo H, Sho M, Kobayashi M, Komatsu M, Kawamura K, et al. Arterial enlargement, tortuosity, and intimal thickening in response to sequential exposure to high and low wall shear stress. J Vasc Surg. 2004;39:601–12.
Sonesson B, Hansen F, Stale H, Lanne T. Compliance and diameter in the human abdominal aorta —the influence of age and sex. Eur J Vasc Surg. 1993;7:690–7.
Struijk PC, Stewart PA, Fernando KL, Mathews VJ, Loupas T, Steegers EAP, Wladimiroff JW. Wall shear stress and related hemodynamic parameters in the fetal descending aorta derived from color Doppler velocity profiles. Ultrasound Med Biol. 2005;31:1441–50.
Sukharev S, Betanzos M, Chiang CS, Guy HR. The gating mechanism of the large mechanosensitive channel MscL. Nature. 2001;409:720–4.
Thoma R. Untersuchungenü ber die Histogenese und Histomechanik des Gefässsytems. Stuttgart: Ferdinand Enke; 1893.
Wagenseil JE, Mecham RP. Vascular extracellular matrix and arterial mechanics. Physiol Rev. 2009;89:957–89.
Weinberg PD, Ethier CR. Twenty-fold difference in hemodynamic wall shear stress between murine and human aortas. J Biomech. 2007;40:1594–8.
Wensing PJ. Arterial tortuosity in the femoropopliteal region during knee flexion. J Anat. 1995;186:133–9.
Wolinsky H, Glagov S.A lamellar unit of aortic medial structure and function in mammals. Circ Res. 1967;20:99–111.
Zamir M. Shear forces and blood vessel radii in the cardiovascular system. J Gen Physiol. 1977;69:449–61.
Zeng Y, Tarbell JM. The adaptive remodeling of endothelial glycocalyx in response to fluid shear stress. PLoS One. 2014;9:e86249.