Chapter 15
Atherosclerosis

Peter R. Hoskins and Patricia V. Lawford

Learning outcomes

1. Describe, in brief, atherosclerosis; the natural history, the clinical consequences for different end-organs and treatment.
2. Describe the effect of a stenosis on haemodynamic quantities; velocity, flow, pressure and wall shear stress.
3. Discuss the variation of flow and blood velocity with degree of stenosis in terms of changes in arteriolar resistance.
4. Describe the mechanical properties of atherosclerotic plaque.
5. Discuss the role of wall shear stress and related phenomena on plaque initiation and growth.
6. Discuss the role of peak cap stress in plaque rupture.
7. Describe in vivo measurements made on atherosclerotic plaque.
8. Describe briefly the treatment of carotid atherosclerosis and of coronary atherosclerosis.

The World Health Organisation reported that in 2012 cardiovascular diseases were responsible for 31 % of all world deaths. The largest contributor to deaths from cardiovascular disease is atherosclerosis. This chapter will explore atherosclerosis, its development, biomechanics and clinical treatment.

15.1 Atherosclerosis

Atherosclerosis is a disease characterised by the build up of fatty deposits in the arterial wall. The disease begins in early childhood and progresses through the entire adult life. There are several stages of atherosclerosis (Lusis 2000) illustrated

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

P.V. Lawford
Sheffield University, Sheffield, England, UK
e-mail: p.lawford@sheffield.ac.uk

P.R. Hoskins et al. (eds.), *Cardiovascular Biomechanics*,
DOI 10.1007/978-3-319-46407-7_15

in Figs. 15.1 and 15.2. Early disease is associated with deposition of fatty deposits (atheroma) within the intimal layer of the wall, initially these are seen as fatty streaks on the inner lumen of the wall (Fig. 15.1b). This is followed by thickening of the intimal layer which may be associated with lipid deposits and the presence of foam cells (Fig. 15.1b). As the disease progresses there is further lipid deposition and an atherosclerotic plaque is formed (Fig. 15.1d). In these initial phases, which may last for many decades, there is preservation of the inner lumen (Glagov et al. 1987). In other words formation of the plaque is associated with outward

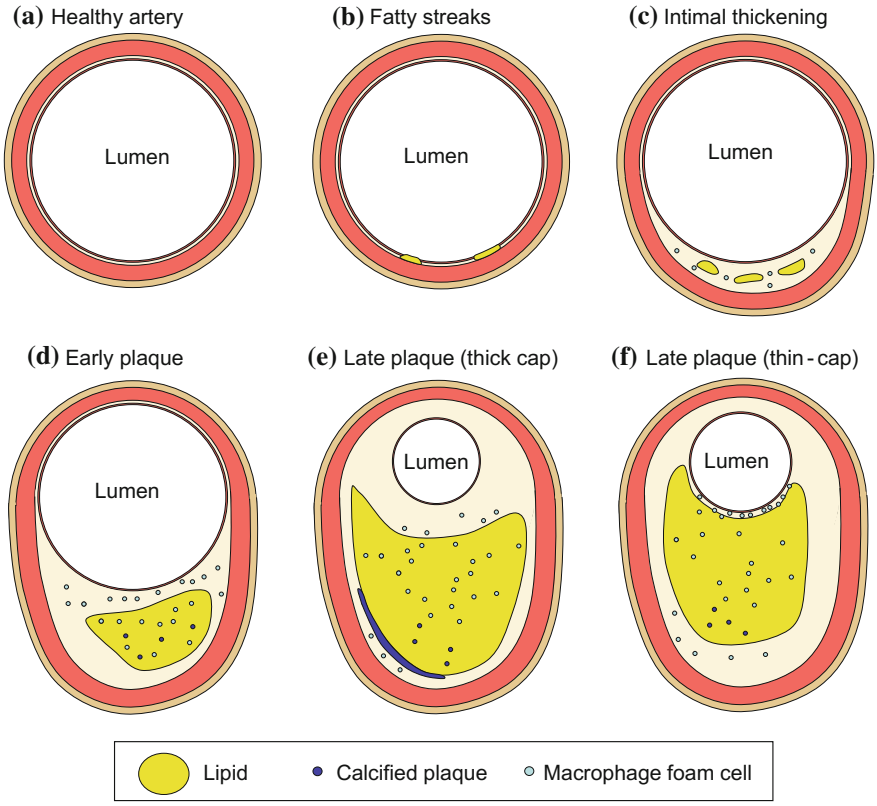

Fig. 15.1 Progression of atherosclerosis with time. **a** Healthy artery showing the various layers, from the outside these are the adventitia, media and intima. **b** The first sign of disease is fatty streaks seen in the intima; these usually appear from about the first decade of life. **c** As the disease progresses there is thickening of the intimal layer; often associated with lipid deposition and the presence of foam cells. **d** An early plaque is formed consisting of a lipid pool, and there are calcified regions, foam cells and cholesterol clefts. The inner lumen is unaffected due to outward remodelling. Early plaque appear from about the third decade of life. **e** and **f** Late plaque is associated with reduction in the lumen diameter; there may be larger regions of calcification. The wall between the lumen and the lipid pool (the cap) is of variable size. In (**e**) the cap is thick, in (**f**) the cap is thin—thin cap plaque are at higher risk of rupture. Late plaque appear from about the fourth decade of life

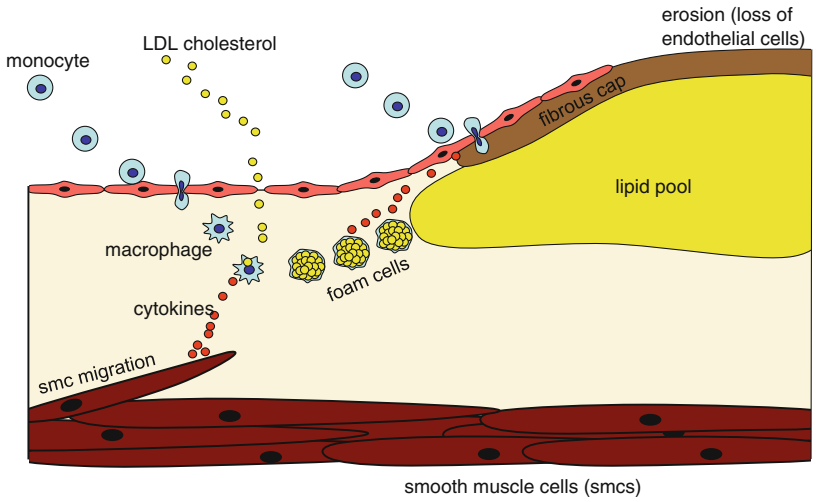

Fig. 15.2 Plaque biology basics. This involves; adhesion of monocytes to the endothelial surface (*1*), migration into the vessel wall (*2*), differentiation into macrophages (scavenger cells) (*3*). Movement of LDL cholesterol between the endothelial cells and into the subendothelial space (*4*) where they are oxidised and ingested by macrophages (*5*) forming foam cells (*6*) which reach a certain size and then rupture depositing their lipids in the vessel wall (*7*) which attracts more monocytes (*8*). Migration of vascular smooth muscle cells (smcs) from the media into the intima (*9*) and smc proliferation under the control of cytokines (*10*)

remodelling of the vessel wall. Later stages of plaque formation are associated with encroachment of the lumen. The degree of narrowing (stenosis) increases with time and there is flow reduction at higher degrees of stenosis. Figure 15.1e, f show late-stage plaque, one with a thick cap (Fig. 15.1e) and one with a thin cap (Fig. 15.1f). It will be described below that cap thickness is a principle determinant of rupture risk. If the plaque ruptures there is spillage of thrombogenic (clot-promoting) plaque contents into the bloodstream which are then carried downstream and can cause blockage of downstream vessels. The ruptured plaque may also become thrombosed further exacerbating reduction in flow.

All these phenomena (local lumen reduction, spillage of contents and local thrombosis) combine to cause reduced perfusion to the tissues supplied by the artery. If perfusion reduces below a critical amount then there is tissue death. The tissue which is affected may have an alternative supply from a different artery in which case perfusion may be impaired but still sufficient for tissue viability. Often plaque rupture is the event that triggers symptoms in the patient. Plaque rupture in the carotid arteries typically leads to death of brain tissue (stroke). Plaque rupture in the coronary arteries typically leads to death of cardiac tissue (heart attack).

For arteries supplying the legs (aorta, iliac, femoral), the effects of atherosclerosis are often less dramatic. As atherosclerosis progresses then a secondary

(collateral) circulation develops which enables blood to bypass the affected artery. The first sign of disease is claudication which is pain in the calf after walking. The distance the patient can walk (the claudication distance) gradually decreases until the patient has pain at rest. Any further deterioration leads to inadequate blood supply which if untreated can lead to tissue death and gangrene.

Treatment of disease is usually associated with re-establishing adequate perfusion, and in some cases surgical removal of dead tissue through amputation. Re-perfusion treatment can involve bypassing the affected artery using a vein taken from the patient or using an artificial graft. The atherosclerotic plaque may be surgically removed if the artery is accessible, such as the carotid artery. The artery may be rebored using catheter techniques under X-ray guidance. Stents may be used in an attempt to stop re-stenosis.

15.2 Biomechanics

Atherosclerosis causes considerable changes to the elastic properties of the vessel wall and to blood flow and pressure which are described in this section.

15.2.1 The Flow-Field in Stenoses

The effect of a stenosis on local blood velocities is illustrated in Fig. 15.3. This is an idealised 70 % stenosis by diameter with steady flow. As the blood flows through the stenosis there is an increase in velocity. This may be understood in that, as the cross-sectional area A decreases, the velocity v increases. The flow rate is the product of the cross-sectional area and the mean velocity

$$Q = Av \tag{15.1}$$

Flow rate is constant at all cross sections along the vessel so that a decrease in A must lead to an increase in v. It might be thought that the maximum velocity would be located at the point of minimum lumen however this is not the case. The convergence of the flow streamlines which occur in the immediate pre-stenotic region continues and the minimum diameter of the flow stream is located just downstream of the minimum lumen; this region is called the ‘vena contracta’. The maximum velocity is located at the vena contracta, not at the point of minimum lumen. Immediately downstream of the stenosis there is a region of flow recirculation. Flow separation occurs and there is a boundary layer separating the two flow regions. The boundary layer reattaches to the vessel wall downstream as shown in Fig. 15.3b

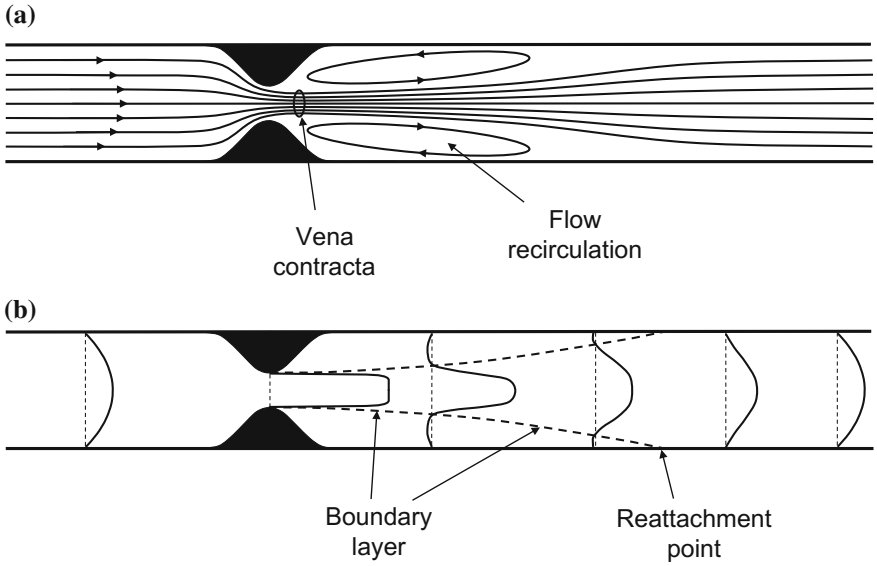

Fig. 15.3 Schematic of flow characteristics in an idealised 70 % stenosis in which turbulence is ignored. Velocity increases within the stenosis and a jet is formed. In the immediate post-stenosis region there is boundary separation with an area of recirculating flow. Fully developed flow is re-established some diameters downstream

Changes in the velocity profiles are shown in Fig. 15.3b. The velocity profile which is initially parabolic becomes almost flat within the stenosis. In the post-stenotic region the velocity profile has small regions of reverse flow. Due to viscosity, the effect of the stenosis on the flow patterns diminishes with distance. After several diameters downstream the jet dies out and the parabolic velocity profile resumes. In this idealised example the effect of turbulence has not been considered, and the region of recirculation is stable. In real stenoses in arteries the post-stenotic region may be highly unstable with turbulence and detachment of the post-stenotic vortices which are swept downstream. Figure 15.4 shows examples of flow-field data taken in simulated stenoses.

The changes which the stenosis makes on the velocity field will cause changes to the wall shear stress patterns (Fig. 15.5). The maximum wall shear stress is located just before the minimum lumen. The post-stenotic region has low wall shear stress values. The peak wall shear stress in the tighter stenosis is 180–200 Pa. These high values of wall shear stress are thought to be responsible for the endothelial stripping which commonly occurs in tight stenoses in vivo. The distribution of wall shear stress is relevant in terms of the growth of atherosclerotic plaque as described in Sect. 15.3.

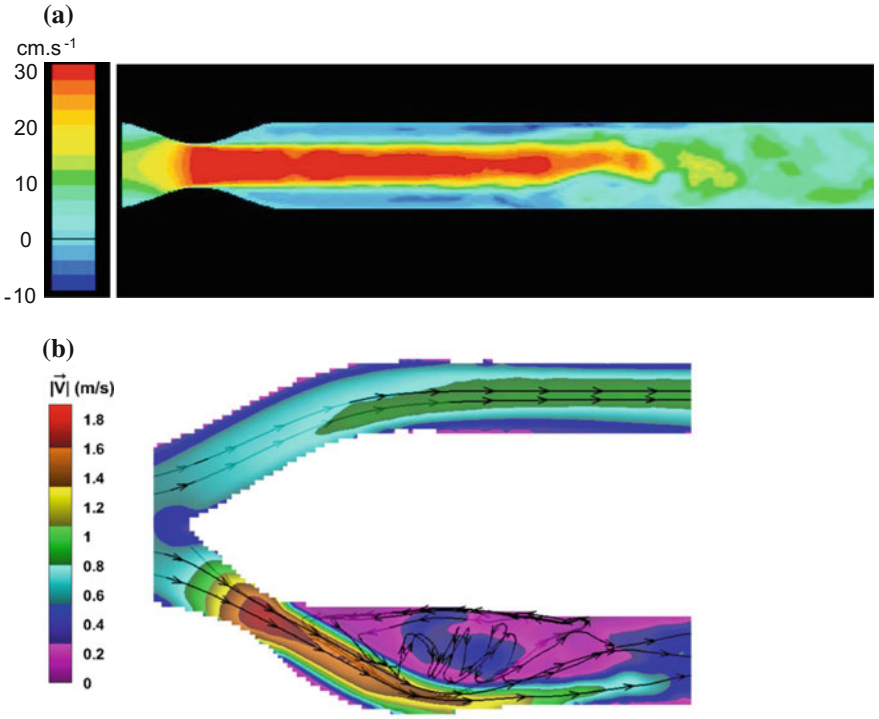

Fig. 15.4 Flow-field data in idealised stenoses. **a** 50 % stenosis with velocities estimated using CFD with an LES model of turbulence. The jet is seen in red with recirculating flow in blue and turbulence several diameters downstream. **b** Planar carotid bifurcation model with a 50 % stenosis with velocities estimated using PIV. The jet is seen in red with recirculation of flow in purple and blue. Figure 15.4b reprinted from; Journal of Biomechanics, Vol. 47(1); Kefayati S, Holdsworth DW, Poepping TL; Turbulence intensity measurements using particle image velocimetry in diseased carotid artery models: Effect of stenosis severity, plaque eccentricity, and ulceration; pp. 253–263, Copyright (2014); with permission from Elsevier

15.2.2 Pressure Changes Across Stenoses

To investigate the change in pressure as blood flows through a stenosis we will initially consider flow of an idealised fluid in which there is no loss of energy in which case the simplified version of Bernoulli's equation can be used

$$P + h\rho g + \frac{\rho v^2}{2} = \text{constant} \tag{15.2}$$

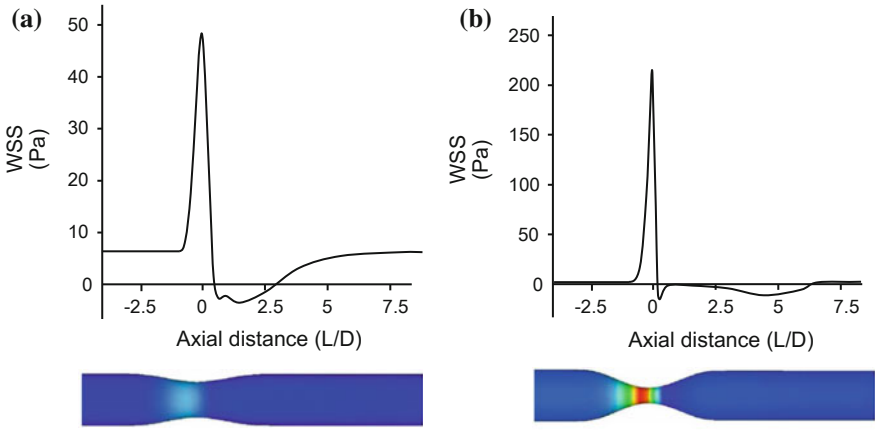

Fig. 15.5 Wall shear stress in idealised stenosed straight arteries estimated using CFD, with **a** 30 % stenosis and **b** 70 % stenosis. In each case the peak wall shear stress occurs just before the point of minimum lumen and there is negative shear stress in the immediate post-stenotic region. WSS images from; Li (2007); reprinted with permission from the author

where P is pressure, h is height, ρ is density, g is the gravitational constant and v is velocity.

Assuming that the effects of gravity can be ignored, this gives, equation, 15.2

$$P + \frac{\rho v^2}{2} = \text{constant} \tag{15.3}$$

In Eq. 15.2 an increase in velocity is associated with a reduction in pressure, and vice versa. As blood flows through a stenosis there will be an increase in velocity and consequently a reduction in pressure (Fig. 15.6b). The point of maximum velocity and minimum pressure is located at the vena contracta. Downstream from the vena contracta the velocity decreases and so pressure increases, eventually recovering to its pre-stenosis value. This may be explained in terms of energy. The energy of the blood is shared between energy associated with pressure and kinetic energy (associated with movement of the blood). In this simplified example the total energy is constant so a reduction in pressure energy is associated with an increase in kinetic energy and vice versa.

In reality there are energy losses due to viscosity and turbulence. This leads overall to a pressure drop as the blood passes through the stenosis as shown in Fig. 15.6c.

Measurements of the pressure drop are widely used in cardiology in the coronary arteries where decisions are made as to which stenosis to treat and whether the effect of treatment has been successful (Sect. 15.5.2).

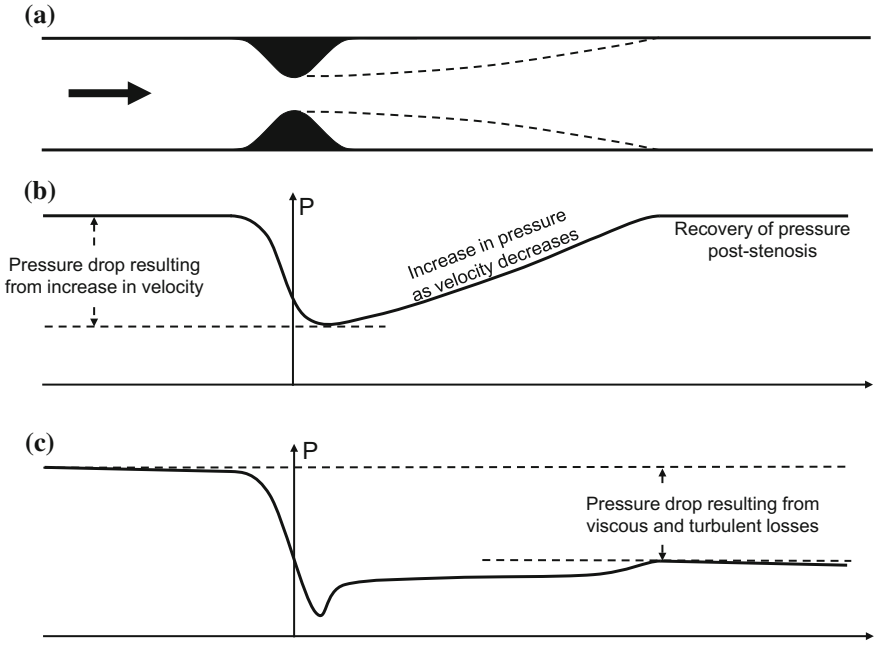

Fig. 15.6 Pressure as a function of axial distance in an artery with a 70 % stenosis (same geometry as Fig. 15.3). **a** Vessel geometry. **b** Flow of blood with no viscosity or turbulence (i.e. no energy loses). The pressure falls reaching a minimum value corresponding to the point of minimum lumen (at the vena-contracta); with increasing distance from the stenosis there is increase in pressure with full recovery to the pre-stenotic value. **c** Flow of blood including energy losses due to viscosity and turbulence. There is some recovery of pressure in the post-stenosis region but overall there is a pressure drop resulting from viscous and turbulent energy losses

15.2.3 Flow Rate and Velocity as a Function of Degree of Stenosis

It might be expected that even a small reduction in artery diameter would cause some reduction in flow rate in the artery. However studies on animals with artificial stenosis and flow monitoring probes have shown that the flow is unaffected until the degree of stenosis reaches about 70 % by diameter (91 % by area), (Berguer and Hwang 1974). The value of lumen reduction after which flow decreases is called the 'critical stenosis'. Figure 15.7 shows the effect of stenosis value on flow rate and blood velocity. The velocity increases from 20 $cm.s^{-1}$ in an unstenosed artery to a maximum value of 600 $cm.s^{-1}$ at 84 % stenosis. It will be described in Sect. 15.4, in terms of clinical measurement of the degree of stenosis, that it is velocity which is used as flow rate does not distinguish different degrees of stenosis.

This data may be explained using the simple model of the arterial system described in Chap. 5, which is shown in Fig. 15.8. The flow rate is determined by

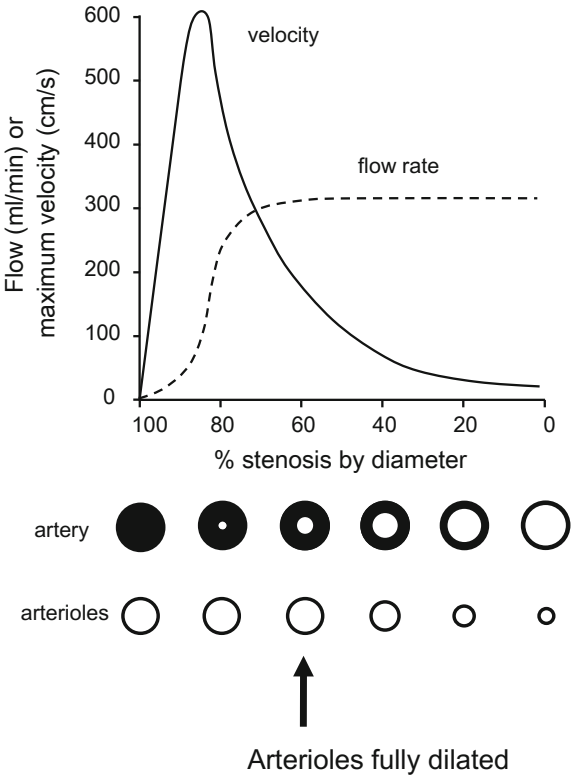

Fig. 15.7 Flow rate and velocity as a function of degree of stenosis. Flow rate is maintained constant up to 70 % by diameter after which flow reduces. The diameter of the artery and downstream arterioles are illustrated. As disease progresses the arterioles compensate by dilating in order to maintain flow constant. At 70 % stenosis the arterioles are fully dilated. Further increase in disease cannot be compensated by further arteriolar dilation and flow reduces. Drawn from data in Spencer and Reid (1979)

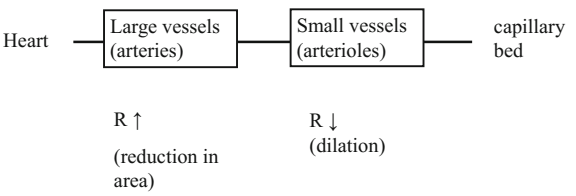

Fig. 15.8 Simple model of flow consisting of a heart, an artery and a downstream arterioles. Disease in the artery increases resistance. This is compensated by decrease in resistance of the arterioles

the pressure gradient and by the overall resistance. The overall resistance is a combination of the resistance in the large arteries and in the arterioles. When a stenosis develops, the resistance in the large arteries increases. This is compensated by a reduction of resistance in the arterioles which is caused by dilation of the arterioles. Hence the overall resistance is maintained constant and the flow rate is also maintained constant. The arterioles are fully dilated when the stenosis value is 70 % by diameter (Fig. 15.7). Further increase in the degree of stenosis leads to increase in overall resistance and the flow rate decreases.

The concept of critical stenosis is useful in understanding the haemodynamic effects of stenosis, however in practice other mechanisms come into play to help preserve perfusion to the organ. The organ may be perfused by several arteries so

that flow reduction in one artery does not have a drastic effect on perfusion. In the brain, the Circle of Willis acts to connect the different arteries which supply the brain. If the Circle of Willis is complete, then a stenosis in one artery (e.g. left internal carotid artery) may have a relatively minor impact on perfusion of the brain as the supply of blood can be taken over by other arteries. However if the Circle of Willis has missing connections then this resupply from other arteries is less effective and there will be reduced perfusion to the relevant area of the brain which may lead to a stroke. Atherosclerosis in arteries in the leg leads to reduction in flow rate in the artery. However, downstream (distal) tissues may be supplied by a collateral circulation which bypasses the diseased region. The collateral circulation consists of many small arteries which grow in size as the degree of stenosis in the main artery increases. The severity of symptoms (claudication, gangrene) depends to a large extent on how well the collateral circulation matures. Patients may have complete occlusion of both superficial femoral arteries and be unaware of this as they have very well developed collateral circulations.

15.2.4 Plaque Stiffness and Wall Stress

From a mechanical point of view an atherosclerotic plaque has two main regions; a lipid pool surrounded by a fibrous region (Fig. 15.9). The region of the plaque between the lipid pool and the lumen is called the 'cap', and rupture of the cap triggers clinical events such as stroke and heart attack. Plaque rupture occurs when the mechanical stress within the cap exceeds the mechanical strength of the plaque. The first studies on the stress distribution within the cap were performed by Richardson et al. (1989), Loree et al. (1992) and Cheng et al. (1993). There have been many subsequent studies which are reviewed in Cardoso and Weinbaum (2014). Figure 15.10 illustrates typical findings from computational stress modelling. The presence of the lipid pool leads to stress concentrations within the cap. The thickness of the fibrous cap also plays a role; thin caps have increased stress. This has led to the idea that vulnerable plaque (those with high risk of

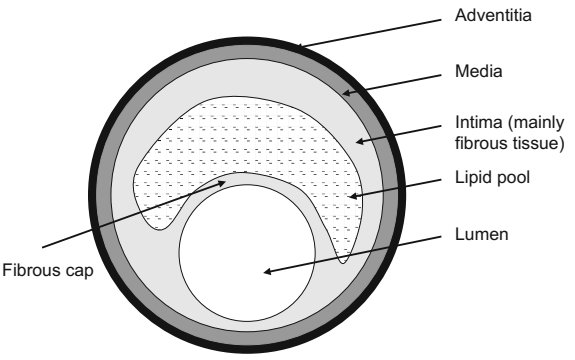

Fig. 15.9 Constituents of an atherosclerotic plaque from a mechanical perspective

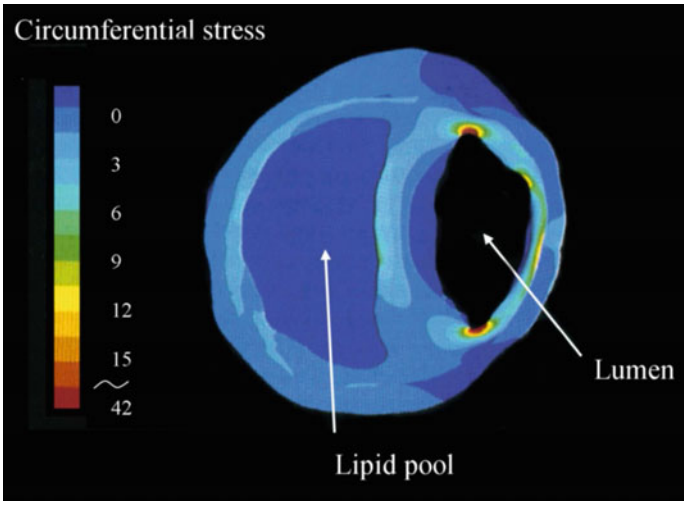

Fig. 15.10 Display of tissue stress (labelled circumferential stress) in a two-dimensional (2D) cross-section of a plaque. The 2D geometry was taken from microscopy of a section of an excised artery. Elastic moduli were taken from the literature and solid modelling used to estimate stress. Stress hot spots are shown at the shoulders of the fibrous cap. From Rohde L, Lee RT. Mechanical stress and strain and the vulnerable atherosclerotic plaque. In: Fuster V, editor. The vulnerable atherosclerotic plaque: understanding. Identification and modification. New York: Futura Publishing Company, 1999: p. 305–316. © Futura Publishing Company. Reprinted with permission from John Wiley & Sons

rupture) have high cap stress as a result of thin cap, whilst stable plaque (those with low risk of rupture) have low cap stress as a result of thick fibrous cap. Microcalcifications within the cap are also thought to play a role in that these act to locally increase the stress due to the differing gradients of stiffness between these microcalcifications and the surrounding fibrous tissue. Early attempts to quantify risk suggested that plaque with a cap thickness less than 65 μm were at risk of rupture (Loree et al. 1992), and that plaque with a peak wall stress greater than 300 kPa were at risk of rupture (Cheng et al. 1993).

The material properties of the individual components of the plaque are required for stress modelling. Table 15.1 shows a summary of indicative values for elastic modulus of plaques as a whole and of the individual components in order to show differences in stiffness of the different components. In practice there are a wide range of values in the literature associated with the variability of plaques, the measurement conditions, and whether a linear or nonlinear stress-strain model is used. The overall stiffness of a plaque will strongly depend on the relative size of the lipid pool. Stable plaque with small or no lipid pool will be stiffer than vulnerable plaque with large lipid pool. This goes some way to explaining the large variation in the overall stiffness of plaque in Table 15.1.

Table 15.1 Elastic moduli of atherosclerotic plaque and plaque components; value (range)

Component	Elastic modulus (kPa)	Reference
Whole plaque	530 (1–2300)	Cardoso et al. (2013)
Lipid	50 (1–202)[a]	Baldewsing et al. (2004)
Smooth muscle cells	1000[b]	Baldewsing et al. (2004)
Collagen	1500[c]	Baldewsing et al. (2004)

[a]Mean of 1, 0.5, 16.4 and 202 kPa, values taken from Cheng et al. (1993), Lee et al. (1996), Veress et al. (2000) and de Korte et al. (2000)
[b]From Lee et al. (1996)
[c]Mean of 630 and 2310 kPa, from Mozersky et al. (1972) and Gow and Hadfield (1979)

The reader is referred to the article by Cardoso and Weinbaum (2014) for a review of plaque stress modelling, mechanical properties of plaque and components, and the thickness of the cap in relation to risk of rupture.

15.2.5 Stenosis Wall Dynamics

Atherosclerotic plaque is associated with local changes in the arterial stiffness. These cause alterations to the local motion of the arterial wall. Figure 15.11 shows

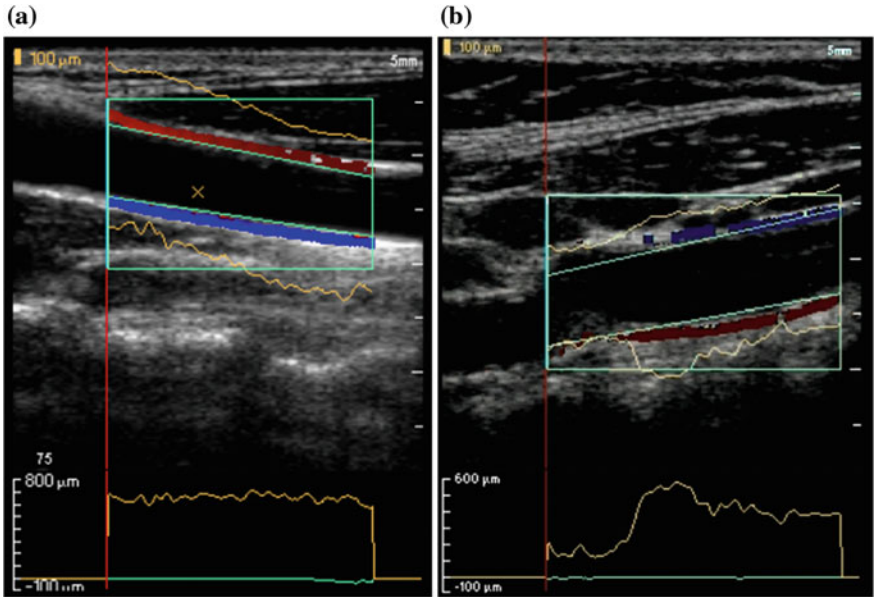

Fig. 15.11 Multi-line wall motion. Top: TDI images and instantaneous wall displacement (magnified). *Bottom*: maximum wall distension. **a** Healthy carotid showing no change in maximum distension with position along the vessel axis. **b** Stenosed artery showing restriction of movement within the region of the stenosis. From; Dineley JA. Doppler ultrasound measurement of arterial wall motion; Ph.D. thesis; Edinburgh: Edinburgh University Library; 2006; reprinted with permission from the author

the wall motion measured using ultrasound in a normal artery and in an artery with atherosclerotic plaque. The normal artery shows uniform displacement as a function of longitudinal position which is expected. The atherosclerotic plaque shows different parts of the wall moving in different directions at the same time. This causes a longitudinal strain which itself may be a potential source of rupture risk.

15.3 Plaque Initiation, Growth and Rupture

This section describes the development of atherosclerosis from initiation through plaque growth and eventual rupture, concentrating on the role of forces.

15.3.1 Initiation of Atherosclerosis

In previous sections it has been noted that the arterial system detects wall shear stress and remodels in an attempt to maintain mean wall shear stress within a narrow bound. Wall shear stress plays a central role in the initiation of atherosclerosis. It was proposed that atherosclerosis is initiated at regions of low wall shear stress (Caro et al. 1971) and regions where the wall shear stress direction changes during the cardiac cycle (Ku et al. 1985). The oscillatory index (OSI) was formulated to capture the pattern of changing direction (He and Ku 1996). Common sites for the initiation of atherosclerosis are on the inner curve of arteries and bifurcations (Figs. 15.12 and 15.13), which are associated with low wall shear stress.

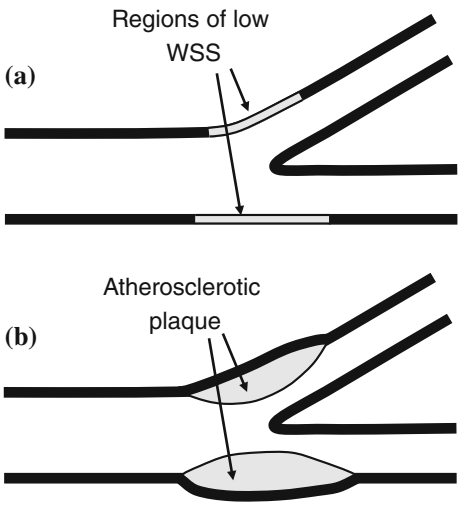

Fig. 15.12 Schematic of a bifurcation showing **a** low shear regions in the undiseased artery, **b** the development of atherosclerotic plaque several decades later

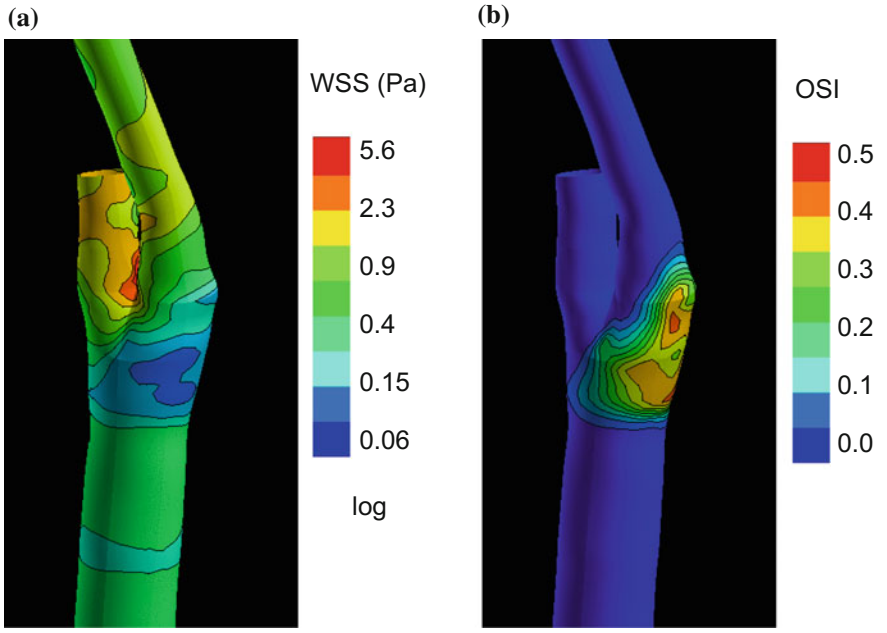

Fig. 15.13 Carotid bifurcation showing **a** mean wall shear stress, **b** oscillatory index. Images kindly provided by Prof. Yun Xu, Imperial College, London

The low WSS / high OSI model has underpinned this area for the last 30 years. A systematic review demonstrated that the actual evidence to support this hypothesis is not strong (Peiffer et al. 2013a) and they proposed that multidirectional wall shear stress is the important initiating feature (Mohamied et al. 2014). The Trans-WSS index was formulated to quantify multidirectional wall shear stress (Peiffer et al. 2013b). A summary of this area is provided by Mohamied et al. (2014).

15.3.2 Plaque Growth and Rupture

Plaque growth is initially associated with preservation of the lumen; that is the plaque grows outwards. This phenomenon was discovered by Glagov et al. (1987). He hypothesised that there is compensatory expansion of the vessel in order to maintain the lumen at a constant diameter. This compensatory expansion is almost certainly as a result of control of mean wall shear stress. In early growth the medial layer increases in size increasing the stiffness of the artery and reducing diameter. The overall flow remains constant but blood velocity and wall shear stress increase as a result of decrease in cross-sectional area. The endothelium, which in this stage of disease is still intact, detects the increase in wall shear stress. The endothelium initiates signalling events which result in increase in diameter to maintain wall shear

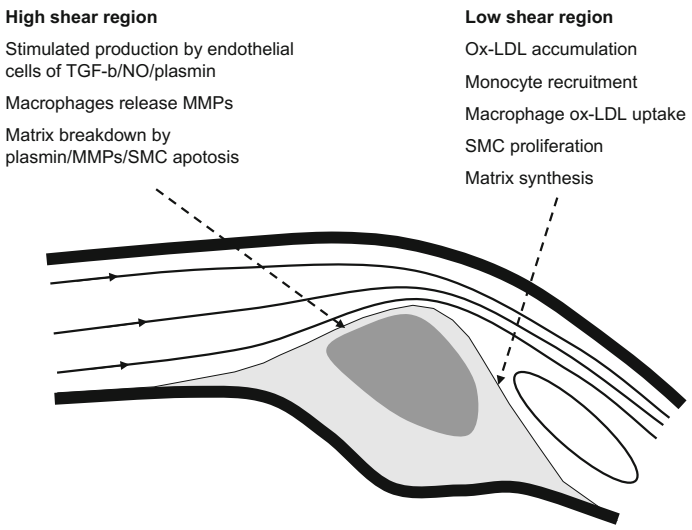

Fig. 15.14 Schematic of an atherosclerotic plaque showing high and low shear regions

stress constant. In practice there is a limit to this process. Outward remodelling continues till the relative plaque area reaches 40 % after which there is lumen reduction and formation of a stenosis. The reasons for this 40 % threshold are unclear (Slager et al. 2005a, b).

As the plaque continues to grow so the degree of stenosis continues to increase. The wall shear stress on the upstream (proximal) side of the plaque increases whilst the WSS on the downstream side of the plaque decreases (Figs. 15.5 and 15.14). These upstream and downstream regions have a different haemodynamic environment and biological behaviour. The following is based on hypotheses formulated by Slager et al. (2005a, b).

In the upstream region of the plaque the high WSS stimulates the endothelium to induce thinning of the fibrous cap. A number of biological processes are triggered including stimulation of macrophages to release MMPs (matrix metalloproteinases) which degrade collagen leading to cap thinning. This is significant in that the cap is then at risk of rupture through high tissue stress. The WSS itself is a tiny force that could not cause cap rupture.

In the downstream region, there is reduced WSS and there may be flow recirculation. In this low shear region there is enhanced recruitment of monocytes (which pass into the wall converting to macrophages). There is also increased residence time of LDL cholesterol and consequently increased transport of LDL into the vessel wall where it is taken up by macrophages, contributing to growth of the plaque.

Overall the haemodynamic environments lead to plaque erosion on the upstream side and plaque growth on the downstream side. It has been observed that in practice plaques tend to grow in the downstream direction (Smedby 1997).

15.4 In Vivo Measurement

This section will provide details of measurement techniques related to arterial mechanics drawing on the principles described in previous sections.

15.4.1 Degree of Stenosis

The degree of stenosis may be estimated from measurements of lumen diameter made from a variety of medical imaging systems, including ultrasound, MRI, CT and X-ray angiography. In clinical practice the degree of stenosis may also be estimated from the maximum blood velocity within the stenosis measured using Doppler ultrasound. The reasons for this are partly historical; early ultrasound systems had insufficiently high image quality to allow visualisation of the lumen. With the improved image quality of modern ultrasound systems lumen may be measured direct in most cases, however estimation via blood velocity remains widely used.

The rationale for using blood velocity is illustrated in Fig. 15.7 where the velocity continuously increases as the degree of stenosis increases, reaching a peak at typically 85 % stenosis by diameter. Figure 15.15 shows a typical image in which maximum velocity is measured. This is then converted to a % stenosis using a standard table; Table 15.2 (e.g. Oates et al. 2009).

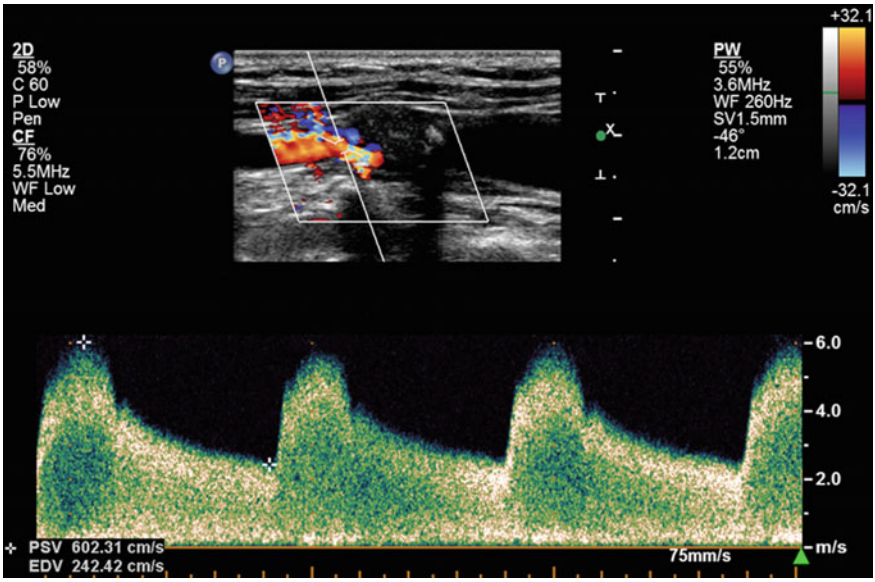

Fig. 15.15 Ultrasound image of a diseased carotid artery. The *upper* image is a composite B-mode image of tissue geometry and a colour image of blood velocity showing increased velocity in the stenosis. The *lower* image show the time-velocity flow waveform. In the example shown the peak velocity is 602 cm.s^{-1}

Table 15.2 Criteria to convert velocity to % stenosis (from Oates et al. 2009)

Peak velocity ($cm.s^{-1}$)	% stenosis (NASCET)
<125	<50
>125	50–69
>230	70–89
>400	>90
Near occlusion	High, low- string flow
No flow	Occlusion

15.4.2 Pressure Drop Across Stenoses

The Bernoulli equation for flow across a small orifice may be written

$$P_1 + \frac{\rho v_1^2}{2} = P_2 + \frac{\rho v_2^2}{2} \tag{15.4}$$

If the velocity v_1 within the orifice is much higher than the velocity v_2 then the v_2 term can be ignored, and the equation becomes

$$P_1 - P_2 = \frac{\rho v_1^2}{2} \tag{15.5}$$

This expression is mostly used to estimate pressure drop across stenosed cardiac valves. It has been used to estimate pressure drop in arterial stenoses but there is poor agreement with invasive measurements and it has been concluded that the simplified Bernoulli equation is not applicable in arteries (de Smet et al. 2000; Illig et al. 1996).

15.4.3 Stiffness

Circumferential stiffness E (Eq. 15.6) and pressure strain elastic modulus E_p (Eq. 15.7) may be estimated from the radial wall motion measured using ultrasound, pressure measured using an arm cuff, and (where possible) wall thickness measured using ultrasound; see Sect. 13.4.1.

$$E = \frac{d_d}{2h} \frac{(P_s - P_d)}{(d_s - d_d)/d_d} \tag{15.6}$$

where h is wall thickness; P_s and P_d are the pressure, and d_s and d_d the diameter, at systole and end-diastole. The elastic modulus is an example of material stiffness.

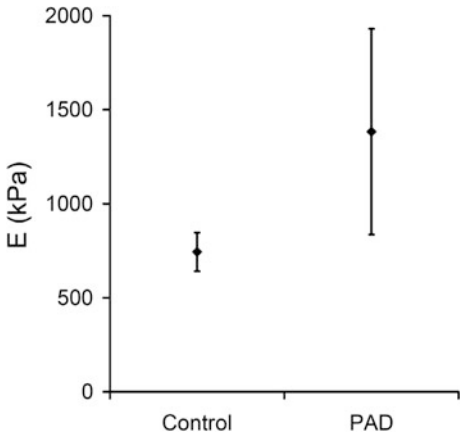

Fig. 15.16 Increase in Young's modulus in carotid arteries in patients with peripheral arterial disease (PAD) compared to controls. Data from Claridge et al. (2009)

$$E_p = \frac{(P_s - P_d)}{(d_s - d_d)/d_d} \tag{15.7}$$

The underlying physical model used in Eqs. 15.6 and 15.7 is an isolated homogeneous ring of uniform stiffness and diameter. This method has been applied to estimate stiffness in patients with atherosclerosis. For example Claridge et al. (2009) identified patients with atherosclerotic plaque in one carotid artery and measured stiffness in the opposite (contralateral) carotid artery. They demonstrated an increase in stiffness in the patients with atherosclerosis compared with normal controls (Fig. 15.16). The assumptions used by the underlying physical model become invalid in advanced atherosclerotic plaque where assumptions of uniformity are untrue.

Stiffness in tissues in vivo may be measured using elastography. This technique was described in Chaps. 9 and 13 where it was noted that the speed of propagation of the shear waves is related to the stiffness of the tissues. This technique has been applied in arteries where images of atherosclerotic plaque show regional changes which are thought to be due to features such as lipid pools.

15.4.4 Stress

The use of patient specific modelling to estimate stress in vivo in carotid plaque was described in Chap. 11; Fig. 11.13, from Gao et al. (2011). The critical cap thickness below which rupture is thought to be likely is 65 μm (see Sect. 15.2.4). This is well below the spatial resolution of an MRI system which is around 250–500 μm. In fact no noninvasive medical imaging system has sufficiently good spatial resolution to adequately resolve the fibrous cap which leads to underestimation of the peak wall

stress. Invasive imaging techniques such as intravascular ultrasound and optical coherence tomography have improved spatial resolutions of 50 and 10–15 μm, respectively, and are used in research studies in plaque visualisation.

15.5 Treatment

The effects of plaque rupture were described in Sect. 15.1 If there is sufficient reduction in blood supply to downstream tissues there will be tissue death (called an 'infarction'), such as occurs in a heart attack or stroke. These events require immediate treatment in order to restore blood flow and prevent tissue damage.

If disease is identified sufficiently early then treatment may be offered before rupture occurs. Patients who have not yet had a major clinical event can be identified by several ways. First they may present to their doctor with more minor symptoms, associated with plaque rupture but which do not lead to infarction. A 'transient ischamic attack' (TIA) or mini-stroke is a brief episode (<24 h) of neurological dysfunction. This includes loss of sight in one or both eyes; lack of coordination; slurring of speech; weakness, numbness or paralysis of one side of the face, arm or leg. A TIA is a warning sign of a possible future stroke. A mini-heart attack is associated with symptoms including difficulty in breathing, chest pains, fainting and vomiting. The second method whereby at-risk patients are identified is through a screening programme if this exists (there are none in the UK for atherosclerosis). The third method is as chance findings whilst the patient is being investigated for other symptoms. In all cases the patient is referred for a series of tests to identify the location and severity of disease and to help decide on the treatment options.

15.5.1 Carotid Disease

Treatment of carotid atherosclerosis is by surgical removal of the plaque; the operation is called 'carotid endarterectomy'. The operation itself carries a risk of stroke so the operation is only offered when the benefit outweighs the risk. Clinical trials were undertaken in the 1990s to establish criteria for selection of patients based on risk. The European Carotid Surgery Trial (ECST collaborators 1998) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET collaborators 1991) both used the degree of stenosis as their diagnostic measure of risk. The measurement methods were slightly different so that current clinical practice (NICE68 2008) is based on surgery if the degree of stenosis is 50–99 % according to NASCET criteria or 70–99 % using ECST criteria. The use of stenting as an alternative to carotid surgery is also undertaken in some patients.

If the degree of stenosis is nonsignificant (<50 % NASCET or <70 % ECST) the patient is offered a combination of medication and advice on changes to lifestyle

aimed at reducing the risk of plaque rupture. Medication includes antiplatelet agents and cholesterol reducing medication (statins). Lifestyle advice includes quitting smoking, changes in diet to reduce cholesterol and increase in exercise.

15.5.2 Coronary Disease

The terms 'coronary artery disease' and 'ischaemic heart disease' describe a single pathology. Ischaemic heart disease is the consequence of a restriction in the flow of blood to the myocardium due to the presence of coronary artery plaque and occurs when the oxygen demands of the heart muscle outstrips the supply. Where ischaemic heart disease is suspected, coronary anatomy is assessed using invasive angiography. Patients with coronary artery disease frequently (but not always) complain of chest pain (angina) and management aims to both to reduce symptoms and to improve outcomes. A first line treatment approach is pharmacological reduction of cardiac parameters such as the preload and afterload. These in turn reduce the workload for the heart and hence myocardial oxygen demand. Vasodilators, betablockers, asprin and statins can also be used to maximise coronary dilatation, reduce myocardial work, reduce the progression of plaque and to stabilise existing plaque, respectively. When this approach fails, patients with uncontrolled angina are offered angioplasty. This technique involves widening of the narrowed artery using a balloon, and often includes the introduction of a metal frame (stent) to support the vessel wall over the longer term. This technique is discussed in more detail in Chap. 17. Patients with severe disease at many different sites within the arteries may be offered surgery (coronary bypass grafting).

A subgroup of patients with ischaemic heart disease will have acute coronary syndrome. These are patients who have already had a myocardial infarction (MI), i.e. an occlusion, and have a high risk of futher plaque rupture and associated MI.

The best management strategies for these different subgroups of patients with cardiac ischaemia, taking account of available evidence, risks and benefits, are in corporated into Guidelines offered by expert groups. An example of these is the widely used European Guidelines (Windecker et al. 2014).

Whilst coronary angiography has become established as the gold standard investigative technique for the diagnosis of coronary artery disease, the decision to treat or not treat individual lesions is often based on the clinician's visual appraisal of angiographic images. Measurement of the fractional flow reserve (FFR) provides a more objective measure of lesion severity (Pijls et al. 1996). The FFR is defined as the ratio of the pressure downstream of the stenosis to the pressure immediately upstream. Pressures can be measured invasively by introducing a catheter with a pressure-sensitive wire into the coronary artery under investigation via the femoral or radial arteries. Recordings are made during maximal flow (hyperaemia). This is achieved by administering a vasoactive drug to dilate the arteries.

$$\text{FFR} = P_d/P_a \tag{15.8}$$

where P_d is the distal (downstream) pressure and P_a is the proximal (upstream) pressure.

As a general rule an FFR of 0.8 or less is taken as an indication that the stenosis requires treatment.

References

Baldewsing RA, de Korte CL, Schaar JA, Mastik F, van der Steen AFW. A finite element model for performing intravascular ultrasound elastography of human atherosclerotic coronary arteries. Ultrasound Med Biol. 2004;30:803–13.

Berguer R, Hwang NHC. Critical arterial stenosis: a theoretical and experimental solution. Ann Surg. 1974;180:39–50.

Cardoso L, Weinbaum S. Changing views of the biomechanics of vulnerable plaque rupture: a review. Ann Biomed Eng. 2014;42:415–31.

Caro CG, Fitz-Gerald JM, Schroter RC. Atheroma and arterial wall shear; observation, correlation and proposal of a shear dependent mass transfer mechanism for atherogenesis. Proc Royal Soc Lond B Biol Sci. 1971;177:109–59.

Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions—a structural-analysis with histopathological correlation. Circulation. 1993;87:1179–87.

Claridge MW, Bate GR, Hoskins PR, Adam DJ, Bradbury AW, Wilmink AB. Measurement of arterial stiffness in patients with peripheral arterial disease: are changes in vessel wall more sensitive than intima-media thickness? Atherosclerosis. 2009;205:477–80.

de Korte CL, Pasterkamp G, van der Steen AFW, Woutman HA, Bom N. Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro. Circulation. 2000;102:617–23.

de Smet AA, Tetteroo E, Moll FL. Noninvasive evaluation before and after percutaneous therapy of iliac artery stenoses: the value of the Bernoulli-predicted pressure gradient. J Vasc Surg. 2000;32:153–9.

Dineley JA. Doppler ultrasound measurement of arterial wall motion; Ph.D. thesis; Edinburgh: Edinburgh University Library; 2006.

ECST (European Carotid Surgery Trial) collaborators. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351:1379–87.

Gao H, Long Q, Kumar Das S, Halls J, Graves M, Gillard JH, Li ZY. Study of carotid arterial plaque stress for symptomatic and asymptomatic patients. J Biomech. 2011;44:2551–7.

Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. New Eng J Med. 1987;316:1371–5.

Gow BS, Hadfield CD. Elasticity of canine and human coronary arteries with reference to postmortem changes. Circ Res. 1979;45:588–94.

He X, Ku DN. Pulsatile flow in the human left coronary artery bifurcation: average conditions. J Biomech Eng. 1996;118:74–82.

Illig KA, Ouriel K, DeWeese JA, Holen J, Green RM. Measurement of carotid bifurcation pressure gradients using the Bernoulli principle. Cardiovasc Surg. 1996;4:130–4.

Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis. 1985;5:293–302.

Lee RT, Schoen FJ, Loree HM, Lark MW, Libby P. Circumferential stress and matrix metalloproteinase 1 in human coronary atherosclerosis—implications for plaque rupture. Arterioscler Thromb Vasc Biol. 1996;16:1070–3.

Li M. Numerical simulation of blood flow and wall stresses in stenosed arteries; Ph.D. thesis; Edinburgh: Edinburgh University Library; 2007.

Loree HM, Kamm RD, Stringfellow RG, Lee RT. Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels. Circ Res. 1992;71:850–8.

Lusis AJ. Atherosclerosis. Nature. 2000;407:233–41.

Mohamied Y, Rowland EM, Bailey EL, Sherwin SJ, Schwartz MA, Weinberg PD. Change of direction in the biomechanics of atherosclerosis. Ann Biomed Eng. 2014;43:16–25.

Mozersky DJ, Strandness DE, Sumner DS, Hokanson DE. Transcutaneous measurement of elastic properties of human femoral artery. Circulation. 1972;46:948–55.

NASCET (North American Symptomatic Carotid Endarterectomy Trial) Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 1991;325:445–53.

NICE68. Clinical guideline 68. Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). July 2008; available from: www.nice.org.uk/guidance/CG68.

Oates CP, Naylor AR, Hartshorne T, Charles SM, Fail T, Humphries K, Aslam M, Khodabakhsh P. Joint recommendations for reporting carotid ultrasound investigations in the United Kingdom. Eur J Vasc Endovasc Surg. 2009;37:251–61.

Peiffer V, Sherwin SJ, Weinberg PD. Does low and oscillatory wall shear stress correlate spatially with early atherosclerosis? A systematic review. Cardiovasc Res. 2013a;99:242–50.

Peiffer V, Sherwin SJ, Weinberg PD. Computation in the rabbit aorta of a new metric—the transverse wall shear stress—to quantify the multidirectional character of disturbed blood flow. J Biomech. 2013b;46:2651–8.

Pijls NH, De Bruyne B, Peels K, et al. Mesurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. N Engl J Med. 1996;334:1703–8.

Richardson PD, Davies MJ, Born GVR. Influence of plaque configuration and stress-distribution on fissuring of coronary atherosclerotic plaques. Lancet. 1989;2:941–4.

Rohde L, Lee RT. Mechanical stress and strain and the vulnerable atherosclerotic plaque. In: Fuster V, editor. The vulnerable atherosclerotic plaque: understanding. Identification and modification. New York: Futura Publishing Company; 1999. pp. 305–16.

Slager CJ, Wentzel JK, Gijsen FJH, Schuurbiers JCH, van der Wal AC, van der Steen AFW, Serruys PW. The role of shear stress in the generation of rupture-prone vulnerable plaques. Nat Clin Pract Cardiovasc Med. 2005a;2:401–7.

Slager CJ, Wentzel JJ, Gijsen FJH, Thury A, van der Wal AC, Schaar JA, Serruys PW. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. Nat Clin Pract Cardiovasc Med. 2005b;2:456–64.

Smedby O. Do plaques grow upstream or downstream? An angiographic study in the femoral artery. Arterioscler Thromb Vasc Biol. 1997;17:912–8.

Spencer MP, Reid JM. Quantitation of carotid stenosis with continuous wave (CW) Doppler ultrasound. Stroke. 1979;10:326–330

Veress AI, Vince DG, Anderson PM, Cornhill JF, Herderick EE, Kuban BD, Greenberg NL, Thomas JD. Vascular mechanics of the coronary artery. Z Kardiol. 2000;89(Suppl 2):92–100.

Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, et al. 2014 ESC/EACTS Guidelines on myocardial revascularisation. Euro Heart J. 2014;35:2541–619.