

## 2 Atherosclerosis II

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### 1. Anatomical Distribution of Atherosclerosis

Atherosclerosis commonly affects the artery only at certain well-defined locations rather than through its entire course. In humans, atherosclerotic lesions usually predominate at the origins of tributaries, bifurcations, and curvatures

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(1, 2) (Fig. 2.1). Some authors (3–9) have thought this focal nature of the disease could be explained by local disturbances in the blood flow. Both the high-shear (3–5) and the low-shear (6–8) areas have been considered as primary sites of atheroma formation. In contrast with these views, we will consider here another view, which is that the *blood pressure–induced arterial wall stress* is the principal factor in the localization of the disease. With this view, we will explore how the arterial mechanics plays a role in this pathology. Pressure load produces mechanical stresses and strains in the entire thickness of the artery wall.

In this regard, we may note that atherosclerotic lesions do not develop in the veins in their normal environment of low pressure and high flow, but that the lesions do develop when the veins are used as arterial bypass grafts where they are subjected to high pressure. Similarly, atherosclerotic lesions develop in the

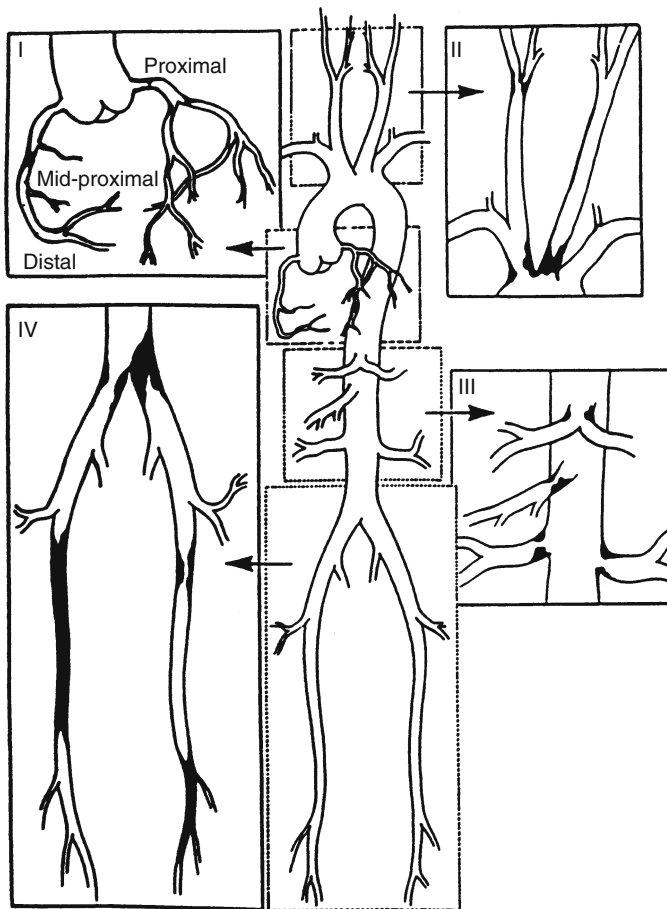


FIGURE 2.1. Distribution of atherosclerotic occlusive disease in humans. (Reproduced from the *Annals of Surgery* 1985;201:116 with permission from Lippincott, Williams & Wilkins, Baltimore, MD.)

pulmonary arteries only in pulmonary hypertension. This is not surprising because high blood pressure in general is a well-recognized risk factor in coronary heart disease, a phenomenon that fits well in the “arterial wall stress hypothesis,” where the stress is produced by blood pressure and not by blood flow.

### *1.1. Atherosclerosis and Functions of the Artery*

To serve as a conduit of blood flow is only one of the basic functions of the artery. The other basic function is to sustain blood pressure. The artery is therefore both, a conduit of blood flow and a container of pressure (pressure vessel). Although the first function has been studied in great detail, the artery as a pressure vessel scarcely has been the subject of investigation. In this chapter, we will attempt to establish that a key to understanding atherosclerosis is to consider the artery as a pressure vessel and as such consider two phenomena relevant to the pressure vessel: 1) stress-concentration at branches and 2) wall fatigue due to pulsatile blood pressure.

### *1.2. Stress-Concentration at the Arterial Branch Origins*

Generally speaking, the stress in the arterial wall produced by luminal pressure may be calculated by the law of Laplace. Accurate determination of stress, however, is complex because the arterial tissue is inhomogeneous and nonlinear, and the artery undergoes significant expansion when pressure is applied.

Figure 2.2a shows a rectangular piece of arterial tissue with a central circular hole under tension. In this situation, the stress exerted upon the tissue is not uniform, but it is concentrated adjacent to the hole at points A and B, which for the same reason will have a predilection to tear. An artery with a side branch (Fig. 2.2b) represents a similar model, which is acted upon by both circumferential and longitudinal stresses, produced by arterial pressure. The stress is greatly increased at both the distal lip and the proximal lip of the branch ostium, which resemble points A and B in Figure 2.2a. Hence, on the basis of the branch geometry alone, the wall stress is increased considerably at the ostial region. This phenomenon of *stress-concentration* is well recognized in the field of high-pressure technology (10), and we have demonstrated its importance both in vitro and in vivo by our observations that the arterial wall stresses indeed are excessive at the branch ostia (11, 12). In our experiments conducted in vitro on the bovine circumflex coronary arteries (Fig. 2.2c), we observed, using finite element stress analysis, that wall stresses are 4 to 6 times higher at the branch orifices at both the proximal and the distal lips of the ostium than in other regions (11, 12). Also, the stress on the inner surface of the artery is the highest and it decreases through the thickness of the arterial wall (11–13). This high stress on the inner surface correlates with the occurrence of atherosclerotic lesions in the intima.

One of the most important consequences of stress concentration at the branch origins is that it produces a greater stretch at that location. In our experiments, we both measured and analytically calculated the stretch in the branch area (Fig. 2.3).

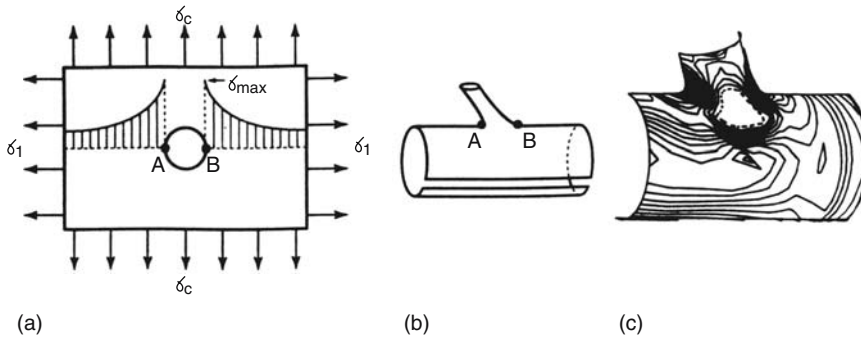


FIGURE 2.2. Stress-concentration at the arterial branch origins. (a) Stress distribution in a rectangular plate with a circular hole.  $\sigma_c$  and  $\sigma_l$  represent, respectively, stresses in the circumferential and longitudinal directions in the artery. The stress in the plate increases toward the hole and reaches a maximum value ( $\sigma_{max}$ ) at points A and B. (b) Schematic presentation of the artery with a branch. When the artery is opened in the longitudinal direction, the ostium of the branch appears similar to the hole in a plate. Points A and B at the ostium are similar to those in (a). (c) Maximum principal isostress contours on the inner surface of a bovine circumflex coronary arterial branch. The wall stress increases from one contour to the next toward the distal and proximal lips of the ostium. The stress was determined in vitro for a pressure increase from 80 to 120 mmHg using a finite element analysis method.

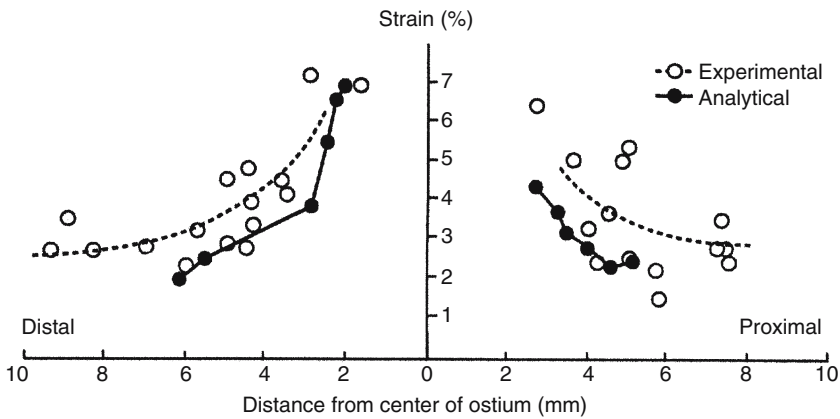


FIGURE 2.3. Distribution of strain around the ostium of a bovine circumflex coronary arterial branch. Experimentally measured strains near both the distal and the proximal lips of the ostium are as high as 5% to 7%, whereas those away from the ostium are 2% to 3%. The analytic strains were obtained from finite element analysis. The strains are for the pressure increase from 80 to 120 mmHg.

The increase in intravascular pressure from 80 to 120 mmHg produced the stretch of 5–7% in the branch region and only of 2–3% in other regions (11). Thus, with each arriving pulse of pressure (120/80 mmHg), the branch region experienced double the amount of stretch compared with the nonbranch regions. This increased stretch in the branch area could influence atherosclerosis through processes such as enhanced low-density lipoprotein penetration or enhanced proliferation of smooth muscle cells.

The stress concentration patterns shown in Figure 2.2c are explored in detail in Chapters 5, 6, and 7. These patterns are generic in nature and therefore applicable to any arterial branch. In other words, there is a stress-concentration present at all arterial branch regions.

## 2. Atherosclerosis and Stress-Concentration

### 2.1. *Ostial Lesions and Stress-Concentration*

Atherosclerotic lesions commonly occur at the ostia of *celiac*, *superior mesenteric*, *right renal*, and *left renal arteries* in the abdominal aorta, especially at the proximal and the distal lips of each ostia (Fig. 2.1). This phenomenon correlates well with the areas of high wall stress and high stretch at the branch as described earlier (Figs. 2.2 and 2.3). Because blood flow induces low shear at the proximal lip and high shear at the distal lip of the ostia, whereas blood pressure induces high wall stress at both the locations, it is logical that pressure-induced wall stress and not flow-induced shear stress correlates with the locations of atherosclerotic lesions.

The occurrence of atherosclerotic lesions in the coronary arteries is of great interest because of its serious consequences. Human coronary arteries also develop severe atherosclerotic plaques predominantly at the branch points. A study on the location of atherosclerotic plaques within the coronary artery bed, based on the casts obtained by injection of a silicone rubber compound, revealed that 78% of the lesions develop at branch sites (14). Similarly, 58% of the lesions were present on the lesser and 35% on the greater curvature of the curved segments. The lesions at the branch sites correlate with the stress-concentration present there (Fig. 2.2), and the lesions on the lesser curvature also correlate with the stress increase there, as we will see in Chapters 4 and 5 and in Section 2.3. The coronary arteries also go through flexion, stretch, and significant changes in their geometry because of the beating heart. All of these changes mean enhanced stretch for the arteries. As we emphasize throughout the book, increased stress and increased stretch are the real stimuli for the cellular proliferation and for atherosclerosis. The occurrence of atherosclerotic plaques at the branch locations in coronary arteries is generally less emphasized in the literature. It is, therefore, important to note that the dominant occurrence of atherosclerosis at the branch in coronaries is similar to the occurrence of atherosclerosis in other arteries.

## 2.2. Aortic Arch Lesions and Stress/Strain Concentration

Figure 2.4 shows the distribution of circumferential strain in the aortic arch. The details of calculations are presented in Chapter 7. Once again, in the aortic arch atherosclerotic lesions seem to be localized at the branch ostia (Fig. 2.1) where the circumferential strains are also localized. Thus, both the concentration of stress or strain can be correlated with the localization of the disease.

## 2.3. Aortic Bifurcation Lesions and Stress

Atherosclerotic lesions in the aortic bifurcation occur at both the “crotch” and the “hip” of the aortic bifurcation (Figs. 2.1 and 2.5). As shown on the bifurcation geometry (Fig. 2.5), the wall stress is very high at the crotch on the basis of the analysis presented earlier in Figure 2.2. Wall stress at the crotch is increased in a manner similar to that at the distal lip of the ostium where the branch angle is small.

To analyze wall stress occurring at the hip of the bifurcation, one must consider three parameters: 1) elliptical cross section, 2) wall thickness, and 3) surface curvatures (Fig. 2.5). Although the cross section of the main aorta and the two iliac arteries is circular, at the bifurcation the cross section becomes larger (15) and

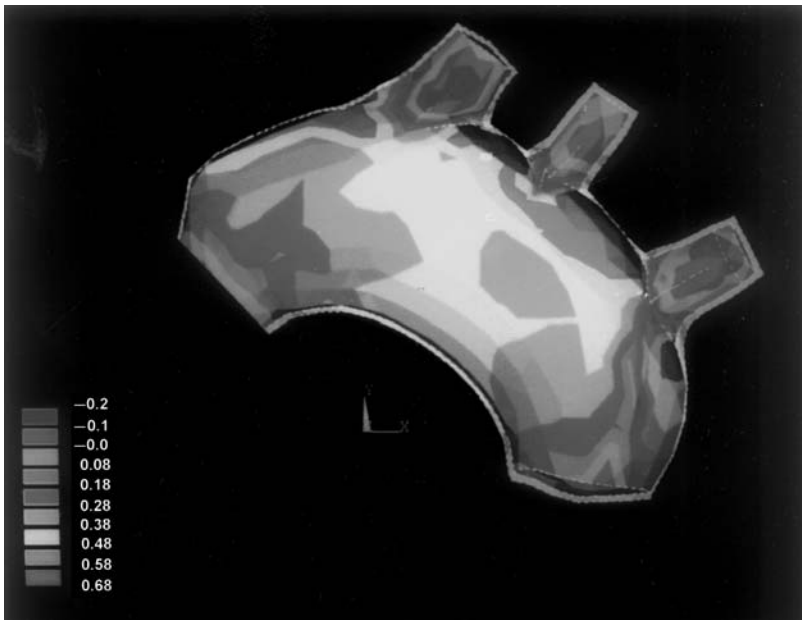
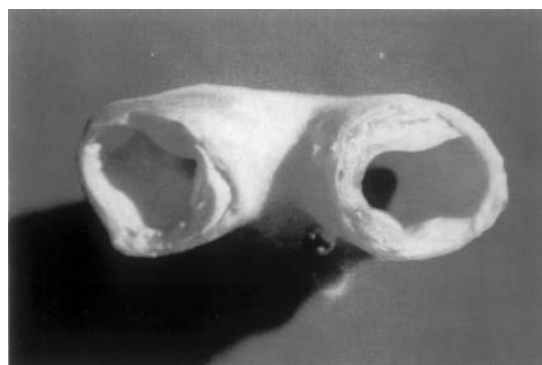
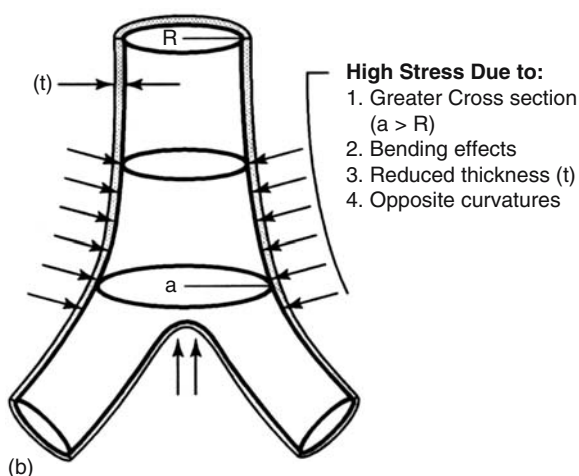


FIGURE 2.4. Circumferential strains in the human aortic arch and great vessels. The strains were determined for a pressure increase from 0 to 100 mmHg using a finite element analysis method. The strains are concentrated around the ostium of branches. See Chapter 7 for details. (Please see color version on CD-ROM.)



(a)



(b)

FIGURE 2.5. (a) Photograph of a human aortic bifurcation showing atherosclerotic lesions at the crotch of the bifurcation. (Reproduced from Texon M, Hemodynamic Basis of Atherosclerosis. Hemisphere Publishing Corporation/Taylor & Francis Inc., Washington, DC, 1980, Plate 10A, with permission.) (b) Schematic presentation showing various geometric parameters that may lead to uneven distribution of stress at the bifurcation. The stresses are high at both the crotch and the hip of the bifurcation. (Please see color version on CD-ROM.)

elliptical. Because the major axis of the ellipse is larger, the wall stress is much higher along the major axis compared with that in the main aorta. In larger aortas, which have higher wall tension, the wall is usually thicker. Thus, thickness of the aorta increases with its diameter and the diameter-to-thickness ratio remains constant; consequently, the wall stress remains constant. In the case of the bifurcation, however, this type of adaption may not occur fully and the thickness is reduced comparatively. As shown in Figure 2.5, the thickness gradually decreases from the main aorta to the iliac artery, and at the hip of the bifurcation the diameter-to-thickness ratio is the highest, leading to further increase in the wall stress. There is another phenomenon associated with the elliptical cross

section. In an elastic artery, the pulse wave tends to change the shape of the cross section from elliptical to circular, which is the lesser energy configuration for the artery wall. This shape change produces additional bending stresses in the wall at the “hip” of the aortic bifurcation. These bending stresses add to the tensile stresses on the inner surface of the artery.

The last stress-enhancing factor we must consider is the arterial curvature (15). What we usually see is that arteriosclerotic plaques often develop on the inner curve of the aortic arch and the inner curve of the tortuous segments of any arteries (16) (Fig. 2.6a). The outer curve is a surface similar to that of a sphere with centers of the two principal radii of the curvatures on the same side of the surface (Fig. 2.6b). The inner surface, on the other hand, has the centers of the two principal radii of curvatures on opposite sides of the surface. It has been well established by Burton (17) and other texts of reference (18) that due to its geometry, the pressure-induced wall stress is much higher on the inner than on the outer curve. This correlates with the observations that atherosclerotic lesions usually favor the inner curve.

At the hip and the crotch of the aortic bifurcation, therefore, the wall stress is increased considerably. This correlates well with the occurrence of atherosclerotic lesions at those locations. The stress analysis of the aortic bifurcation is described in greater detail in Chapter 5.

#### 2.4. Carotid Bifurcation Lesions and Stress

Studying the pathological anatomy of carotid bifurcation lesions, we found that most frequently the less advanced lesions occurred in the sinus bulb area, whereas the more advanced atheromas involved the crotch as well as the entire bifurcation (19) (Fig. 2.7). These observations agree with those reported in the literature (20, 21) and may be explained readily by the distribution of wall stress.

Figure 2.7c shows the geometric parameters that are responsible for producing uneven distribution of the wall stress just as it was the case in the aortic bifurcation. The elliptical cross section at the bifurcation produces high stresses in the “hip” region (areas A and C) as explained earlier. The thickness variation is another important parameter in the current case. The carotid sinus bulb happens to be unusually thin, even thinner than the wall opposite to it. This thin area of the sinus bulb is also the region that has baroreceptors. Obviously, this enhances its sensitivity to pressure because it could stretch more in response to pressure. The reduced wall thickness causes a significant increase in wall stress in the sinus bulb.

A word about baroreceptors may be in order. By far, the best known mechanisms for arterial pressure control is the *baroreceptor reflex*. Basically, this reflex is initiated by stretch receptors called baroreceptors. A rise in pressure stretches the baroreceptors and causes them to transmit signals into the central nervous system, and feedback signals are then sent back through the autonomic nervous system to the circulation to reduce arterial pressure downward toward normal level. Baroreceptors are spray-type nerve endings lying in the walls of the arteries and they are stimulated when stretched. Baroreceptors are extremely abundant in 1) the wall of each internal carotid artery in the area of the carotid

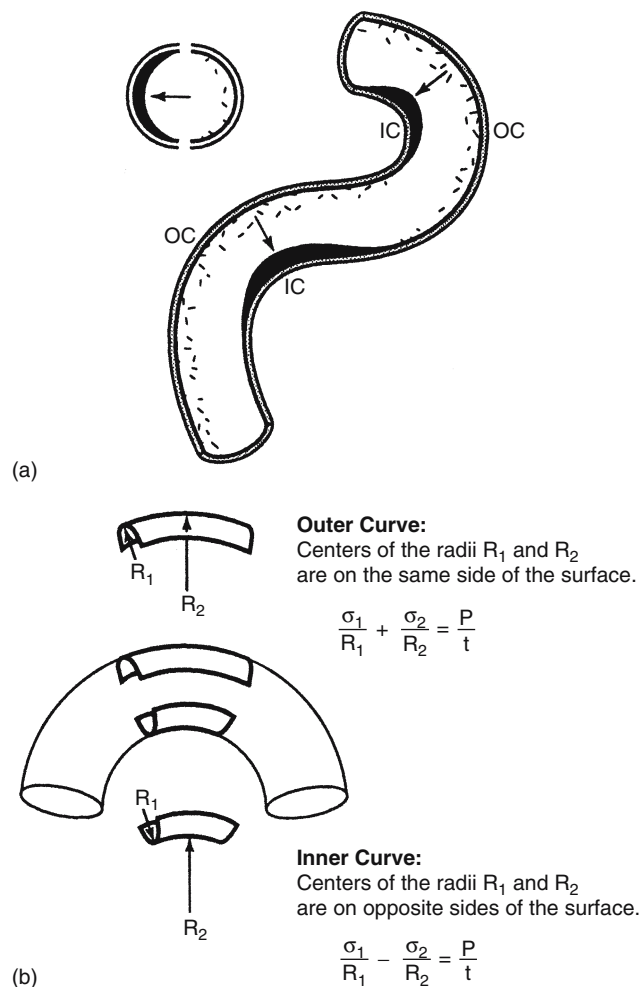


FIGURE 2.6. (a) Longitudinal section of the right carotid siphon, which illustrates the location of intimal cushion (IC). In childhood, the subendothelial elastic layer is well developed along the outer walls (OC) of the curvatures, whereas prominent intimal cushions (arrows) consisting mainly of loose connected tissue and sparse elastic elements are present along the inner walls of the curvatures. Inset shows a cross section of the vessel at the site of the arrows. (Reproduced from Wolf S, Werthessen NT, eds. Dynamics of Arterial Flow. Advances in Experimental Medicine and Biology, Vol. 115. Plenum, New York, 1976:357, with permission.) (b) Stress distribution in a curved artery:  $\sigma_1$  and  $\sigma_2$  represent, respectively, the circumferential and longitudinal stresses. The outer curve is part of a synclastic surface and the inner curve is part of an anticlastic surface.  $P$  represents luminal pressure and  $t$  represents wall thickness. Circumferential stresses are higher on the inner curve than on the outer curve.

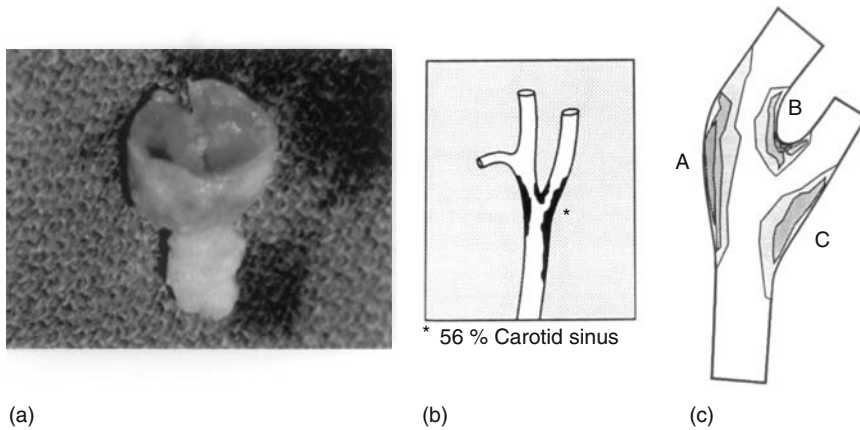


FIGURE 2.7. (a) Atherosclerotic plaque removed from a human carotid artery bifurcation. (b) Locations of atherosclerotic disease at the carotid bifurcation; 56% indicates the relative frequency of occlusive lesions in the brachiocephalic vascular system. Most often, the occlusive lesions occur involving the entire carotid bifurcation (a). (c) Maximum principal isostress contours at the human carotid artery bifurcation. The stresses are high at all three locations, B, A, and C, being the highest at B. The stress contours were obtained from the finite element analysis for a pressure (pulse) loading of 40 mmHg. See Chapter 6 for details. (Please see color version on CD-ROM.)

sinus bulb and 2) the wall of the aortic arch. As stated earlier, both the carotid sinus and the aortic arch are extra stretchable and that would make them prone to atherosclerosis.

We performed a stress analysis on the human carotid artery bifurcation using the method of finite element analysis (19). The results of this analysis are shown in Figure 2.7c. We found that the highest stress occurs at the crotch of the bifurcation, then in a decreasing order at the sinus bulb over a substantially large area and finally at the wall opposite the sinus bulb. Thus, the early lesions in the sinus bulb area as well as the advanced lesions involving the crotch and the entire bifurcation correlate well with the areas of high wall stress. The details of the stress analysis of the carotid artery bifurcation can be found in Chapter 6.

### 2.5. The Descending Thoracic Aorta Lesions and Flexion Stress

In the descending thoracic aorta also there is a well-defined pattern of atherosclerotic lesion development. Cornhill (2) and others (22) have described that lesions in this segment occur in the form of two parallel streaks that run along the sides of the intercostal arteries (Fig. 2.8). The flow pattern does not explain this localization but the wall stress hypothesis suggests that because the descending thoracic aorta is tethered to the spine by means of several pairs of intercostal

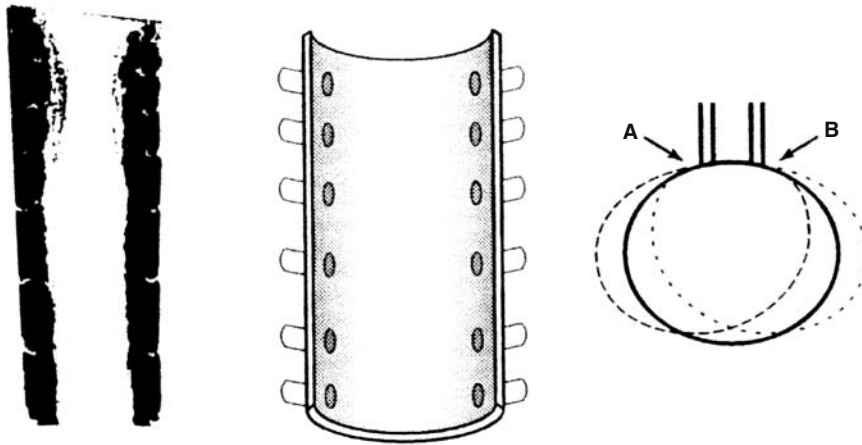


FIGURE 2.8. (Left) Distribution of atherosclerotic lesions in the thoracic aorta in humans. The lesions are present along two parallel lines just on the outside of the pairs of intercostal arteries. (Reproduced from Cornhill JF et al.: In Liepsch DW (ed): Monogram on Atherosclerosis, 1990; 15:15, published by S. Karger AG, Basel, Switzerland, with permission.) (Right) Thoracic aorta in the cross section where the intercostal arteries originate. Any lateral movement of the aorta will be achieved by deformation in regions A and B (i.e., flexion along the two parallel lines). These parallel lines correspond with those along which atherosclerotic lesions develop (left).

arteries, the wall stress may be responsible for this phenomenon. These pairs act as anchors for the aorta so that when the aorta bends during body movement, it changes shape along the two parallel lines by the sides of the intercostal arteries as shown in Figure 2.8. Thus, once again the parallel lines of mechanical flexion of the aorta correlate with the parallel streaks of atherosclerotic lesions.

## 2.6. Effect of Blood Pressure and Lesions in the Lower Extremities

It is well recognized that *elevated blood pressure*, which causes high wall stress, enhances atherosclerosis. As was mentioned earlier, atherosclerosis does not develop in veins under venous pressure but it does when the veins are subjected to arterial pressure. Similarly, atherosclerosis does not develop in *pulmonary arteries* under normal pressure, but it does in pulmonary hypertension. *Lower extremities* are more prone to atherosclerosis than upper extremities, and this also correlates with the pressure, because lower extremities have higher absolute pressure, due to the hydrostatic pressure head, than do the upper extremities (23).

The effect of blood pressure on atherosclerosis seems to be overwhelming in many respects. The pulmonary artery, for example, does not develop atherosclerotic

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plaques even if serum cholesterol levels are very high (400–500 mg/dL). On the other hand, the same vessels may develop severe atherosclerotic plaques, even in subjects with less than 200 mg/dL serum cholesterol, in the presence of *pulmonary hypertension*. Intimal thickening was consistently detected in the aorta immediately after birth, but it was only the pulmonary artery of the elderly individuals that presented similar thickening. Thus, aortic pressure of 120/80 mmHg can be considered atherogenic while pulmonary pressure of 25/10 mmHg does not have an atherogenic character (24).

In patients with *coarctation of the aorta*, there exists a severe hypertension in the brachial but not in other arterial beds. Postmortem examinations revealed extensive atherosclerosis in the areas subjected to hypertension making it possible to see a clear delineation between hypertensive arterial beds and nonhypertensive arterial beds in the same individual. In experimental animals also, a clear increase in atherosclerosis is seen in the artery proximal to coarctation and a decrease is seen distal to coarctation, when the stenosis is sufficient to cause an increase in pulse pressure of 30 mmHg or more in the proximal segment (24–26). Obviously, the most direct effect of pressure increase is the stress increase in the artery wall.

### 3. Atherosclerosis in the Aortic Valve and Stress

It needs to be stated that the diseases of the aortic valve, such as aortic stenosis and insufficiency, may not be related to atherosclerosis, however, the process of atherosclerosis has been implicated in the calcification of the valve cusps (27). Our interest in this section is to examine important observations made by Thubrikar et al. (28) on atherosclerotic lesions of the aortic valve in cholesterol-fed rabbits and how that might relate to the mechanical stress in the valve leaflets.

#### 3.1. Methodology

Eight adult (3.2–4 kg weight, 6–8 months old) New Zealand white rabbits were fed a 2% cholesterol diet for 3–33 weeks. After that, the rabbits were sacrificed and the aortic valve, the aorta, and the major arteries were pressurized and stained with Sudan IV stain. The left ventricle was also flushed and stained with Sudan IV so as to stain the ventricular aspect of the aortic valve leaflets. The aortic valve and the arteries were fixed with 4% formaldehyde, in situ, under a diastolic pressure of 70 mmHg. The aortic valves were then dissected and photographed to record the stained areas. Finally, valves were sectioned and stained with hematoxylin and eosin for histologic examination.

In order to study the pressure-bearing area and the redundant area of the aortic valve leaflets, silicone rubber casts of the aortic valves were made under a diastolic pressure of 70 mmHg. To determine the stress in the aortic valve leaflet, they measured 1) the radius of the leaflet from silicone rubber casts, 2) the thickness of the leaflet, and 3) the pressure gradient across the leaflets. The details of the technique can be found in Ref. 28.

### 3.2. Findings

In rabbits fed with cholesterol diet, Thubrikar et al. found that fatty lesions, demonstrated by Sudan staining, developed in arteries and aortic valves after 3–6 weeks (28). In the major arteries, fatty lesions occurred primarily at arterial branching points. In the aortic valve, lesions appeared in load-bearing areas of the leaflets but not in redundant portions (Fig. 2.9). A histologic section shows the location of a 10-week fatty lesion (Fig. 2.10a). The fatty lesion was more cellular than deeper tissues of the leaflet and extended from the base of the leaflet to the fold between redundant and load-bearing areas of the leaflet. It was confined to the aortic surface of the leaflet. No such lesion was apparent on the ventricular surface of the leaflet at 10 weeks. The redundant part of the same leaflet was similarly free of cellular lesions on both faces. The lesion on the aortic face (Fig. 2.10b) consisted of a mass of so-called foam cells and less numerous cells of a second type in a dense feltwork of collagenous fibers. Foam cells in the fatty plaque were moderately large with relatively round or oval euchromatic nuclei and multiglobular, fatty or foamy cytoplasm. The second type of cells, in contrast, usually had darker nuclei and only one or two prominent cytoplasmic fat droplets, which might in turn impinge on and misshape the nucleus. In these features, the second cell type resembled fibroblasts of the deeper-lying leaflet tissue.

The initial atheromatous plaque appeared between 3 and 6 weeks in tissues of the aortic face at the base of the leaflet and consisted mainly of foam cells. After 7 weeks, the lesion had spread up the wall of the aortic sinus and farther out in the leaflet. Again, only the pressure-bearing portion of the aortic face of the leaflet was affected. By 10 weeks, all leaflet tissues were being affected but not in the same manner. The primary fatty plaque was still confined to the upper aortic face, but fibroblasts of the leaflet, both within its dense fibrous layer and in its

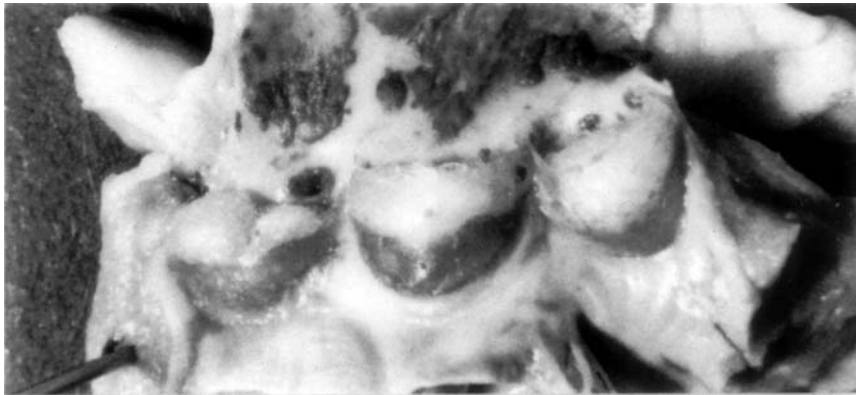


FIGURE 2.9. Photograph of the aortic valve from a rabbit on a 2% cholesterol diet for 11 weeks. Dark areas indicate fatty lesions on the aortic valve, in the coronary arteries, and in the ascending aorta. Fatty lesions occurred only on the load-bearing part of the leaflets.

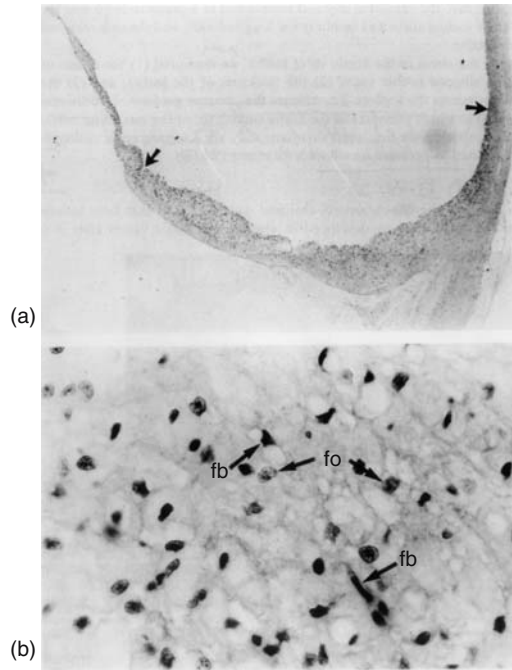


FIGURE 2.10. Histological details from the aortic valve of a rabbit on the cholesterol diet for 10 weeks. (a) Section cut in the radial plane of the leaflet, with free edge of the leaflet to the upper left and aortic sinus to the upper right. A fatty lesion occupies the aortic surface of the leaflet (between arrows). The lesion is characterized by large numbers of foam cells, the nuclei of which appear as dark dots. (b) Portion of the fatty lesion enlarged to show foam cells (fo) and fibroblasts (fb). Foam cells are characterized by a cytoplasm filled with small droplets of fatty material, providing the foamy appearance and have a large, lightly stained nucleus. Fibroblasts tend to be elongated cells with densely stained nuclei and may contain one or two large vacuoles from which lipid has been extracted by the preparation technique.

spongy loose tissue near the ventricular surface, had also taken up fat in one or two large droplets. Even after 33 weeks, the atheromatous plaque had not spread beyond the pressure-bearing aortic face of the leaflet, leaving the redundant portion unencumbered.

The aortic pressure was 90/80 and 85/65 in the two rabbits. The thicknesses of the valve leaflets in these two rabbits were 0.1 mm and 0.12 mm. A study of silicone rubber casts of the closed aortic valves indicated that the pressure gradient was sustained by only part of the leaflet (Fig. 2.11); the rest of the leaflet (its redundant area) was under no pressure gradient. Because the redundant part of one leaflet came in contact with similar parts of the other two leaflets (Fig. 2.12a), diastolic pressure existed on both sides of this part, thereby eliminating the diastolic pressure gradient across it. Casts of the valves of the rabbits

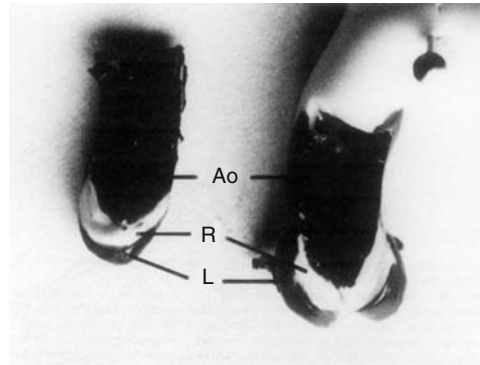


FIGURE 2.11. Photograph of a silicone rubber cast of the aortic valve from a rabbit. In order to visualize the leaflets clearly, a leaflet, sinus, and part of the ascending aorta (Ao) were cut away from the cast and displayed on the left. Also, parts of the casts were painted dark to clarify details of the valve geometry. One leaflet in its entirety and halves of the other two leaflets can be seen. L and R indicate load-bearing and redundant portions of a leaflet, respectively.

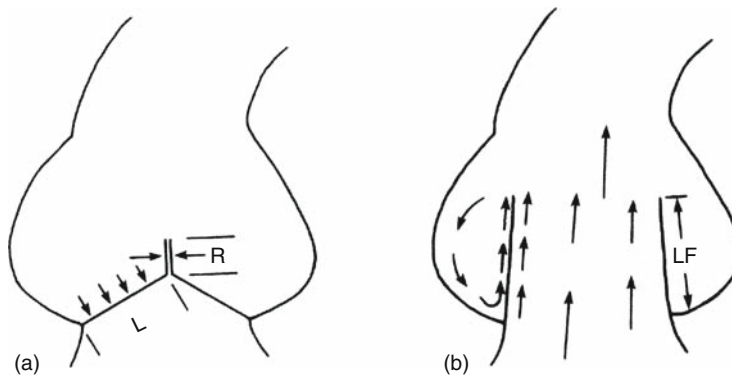


FIGURE 2.12. Schematic drawings of the rabbit aortic valve in the closed (a) and open (b) positions. (a) In the closed valve, only the load-bearing part (L) of the leaflet sustains a pressure gradient across it. The redundant part (R) of the leaflet has pressure on both sides of it and therefore sustains no pressure gradient. L and R in this figure also correspond with L and R of Figure 2.11. (b) Due to forward flow of the blood (central arrows), shear stress occurs on the entire ventricular surface of the leaflet (LF). Similarly, due to vortex formation in the sinus behind the leaflet, shear stress occurs on the entire aortic surface of the leaflet. Only two leaflets are shown for clarity although the valve has three leaflets.

on the cholesterol diet demonstrated that the area occupied by the lesion was the same as the load-bearing area of the leaflet. The silicone rubber casts of the closed aortic valves also showed that the leaflets in the load-bearing part are cylindrical. The radii of the cylindrical leaflet in the two rabbits were 2.3 mm and 2.5 mm.

### 3.3. Stress Determination

In previous studies using dogs, Thubrikar et al. have demonstrated that the orifice of the aortic valve during systole is circular (29, 30). If we assume that aortic valves in dogs and rabbits open in the same way, then the orifice of the opened valve in rabbits should also be circular. Hence, in rabbits, the leaflets of the valve are cylindrical in systole, as their load-bearing part was in diastole. Furthermore, because these leaflets are quite thin, they are likely to behave as a membrane. Therefore, intramural stress (wall stress) in the leaflet may be determined using the equation for stress in a cylindrical membrane (31).

$$\text{Hoop stress (circumferential)} = \frac{PR}{t} \quad (1)$$

where  $P$  is the pressure gradient across the membrane,  $R$  is the radius of a cylinder, and  $t$  is the thickness of the membrane. The stress in the leaflet is 23 g/mm<sup>2</sup> during diastole (using  $P = 70$  mmHg,  $R = 2.4$  mm, and  $t = 0.1$  mm) and 1.6 g/mm<sup>2</sup> during systole (using  $P = 5$  mmHg,  $R = 2.4$  mm, and  $t = 0.1$  mm). This approach to stress determination has been used previously for dog valves (32), and the values obtained here compare favorably with those for the dog. In fact, it is of interest to note that in spite of the difference in size between valves of the rabbit and the dog, the stress in valve leaflets is similar and is highest in the load-bearing part of the leaflet. A significant amount of stress also occurs along the area of attachment of the leaflet, primarily due to flexion of the leaflets as the valve opens and closes. Although this stress has not been determined in the current study, it has been determined previously for dog valves where it was shown that compressive stresses occur along this area (33).

### 3.4. Correlation with Stress

Concerning the localization of atherosclerotic lesions, it has been thought for some time (34, 35) that the occurrence of these lesions at arterial branch points can be attributed to a disturbance in the flow of blood at the branches. Such an explanation applied to aortic valve leaflets does not account for the observations that fatty lesions occur only in load-bearing areas of the leaflets. For example, from Figure 2.12b it can be seen that in systole, shear stress occurs on the entire ventricular surface of the leaflets as the blood flows out of the ventricle. Similarly, shear stress occurs on the entire aortic surface of the leaflet due to vortex formation in the aortic sinuses (36). In diastole, eddy formation from backflow of blood can produce shear stress on the entire surface of the leaflet, and turbulent flow in the ventricle as it fills can produce shear stress on the ventricular surface of the load-bearing part of the leaflet. Thus, at no time in the cardiac cycle is there shear stress present only on the load-bearing part of the aortic surface of the leaflet where fatty lesions preferentially developed.

Occurrence of the lesions can, however, be explained by the intramural stress that occurs due to the pressure gradient across the valve leaflets. The intramural

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stress in the load-bearing area in diastole is approximately 15 times greater than the stress in the entire leaflet during systole. Furthermore, occurrence of early stages of the lesions in the area of leaflet attachment can be correlated with the large degree of flexion there. Even after a long period of high-cholesterol diet (33 weeks), the atherosclerotic lesions of the valve were confined to the load-bearing area of the leaflet, reinforcing the implication that wall stress due to pressure is important in this process.

#### 4. How Stress and Stretch Might Influence Atherosclerosis

Endothelial injury, lipid accumulation, and smooth muscle cell proliferation are essential steps in atherosclerosis. There are several observations that link arterial wall stress and stretch to these processes. For example, endothelial cell morphology was observed by us (37) and by others (38, 39) to be different in the branch regions compared with that in the nonbranch regions (see Chapter 8). Cell culture studies on endothelial cells have established that cells orient in response to cyclic stretch so that their long axis is perpendicular to the direction of stretch (40, 41). The cells also proliferate at a higher rate (42) and show development of stress fibers (41) in response to stretch.

Low-density lipoprotein uptake in the artery also has been studied by us (43) and by others (44). We observed that low-density lipoprotein accumulation in the artery is greater in the branch region than in the nonbranch region (see Chapter 8).

The effect of cyclic stretch on smooth muscle cell proliferation also has been studied. We have observed smooth muscle cell proliferation of severalfold when the artery was de-endothelialized and stretched by a balloon compared with when the artery was only de-endothelialized but not stretched (45) (see Chapter 9). Similar observations have been reported by others (46). Cell culture studies on smooth muscle cells also have established that the cell orientation (47) and other cell functions are influenced by the cyclic stretch (48).

These observations suggest a strong relationship between wall stress, wall stretch, cyclic stress, cyclic stretch, and many cellular processes that are an essential part of atherosclerosis.

#### 5. Existing Concepts of Pathogenesis of Atherosclerosis

The development of a coherent theory of origin and progression of atherosclerosis is compromised by lack of agreement about what constitutes the early stage and to some extent by a lack of consensus on the true nature of the lesions (49). Some see lipid in the lesions as the key to the initiation and progression of the disease, whereas others are more impressed by the proliferative aspects, especially the proliferation of SMCs, and yet others see the inflammatory nature of lesions as a central process. Still others attempt to combine all of these aspects, maintaining that the diversity of the disease results from its multifactorial nature.

### 5.1. Response-to-Injury Hypothesis

Currently, the most widely accepted theory explaining the initiation and development of the disease is the so-called modified response-to-injury hypothesis (49). Table 2.1 shows both, the response-to-injury and modified response-to-injury hypotheses. In the original hypothesis, endothelial injury or dysfunction is the primary event, which is followed by the migration and proliferation of medial SMCs, which form an intimal plaque, which subsequently accumulates lipid. In the modified hypothesis (lipid hypothesis), lipoprotein entry into the intima is the initial event. The monocytes are then attracted to the areas of lipid deposition. The uptake of lipoprotein by monocytes then results in macrophage-rich fatty streak lesion.

The problem with this explanation is twofold: first, not all fatty streaks become lesions; second, many patients with significant atherosclerosis do not have elevated blood lipid levels. Furthermore, early human lesions and fatty streaks contain an overwhelming amount of SMCs. The theory seems more applicable to experimental atherosclerosis created by feeding a high-cholesterol diet to rabbits, for example (49).

TABLE 2.1. Comparison of response-to-injury hypothesis and modified response-to-injury hypothesis.

Response to injury	Modified response to injury
Endothelial injury or stimulus causes release of PDGF or EDGF	Monocytes adhere to endothelium and enter the intima
↓	↓
Smooth muscle cells migrate from media and proliferate in intima	Lipid accumulates in macrophages in the intima
↓	↓
Lipoproteins form complexes with structural proteins, e.g., proteoglycans	Fatty streak disrupts endothelium
↓	↓
Lipoprotein-proteoglycan complexes taken up by smooth muscle cells and macrophages	Platelets adhere and release PDGF
↓	↓
Plaque composed mainly of lipid-laden smooth muscle cells	Smooth muscle cells migrate from media and proliferate in intima
	↓
	Plaque composed mainly of macrophage foam cells with smooth muscle cells at base

EDGF, endothelial cell-derived growth factor; PDGF, platelet-derived growth factor.

## 6. A New Hypothesis for Pathogenesis of Atherosclerosis: Smooth Muscle Cell Injury Hypothesis

A new hypothesis is proposed by Dr. Thubrikar (the author) in this section. This hypothesis is being proposed for the first time. It is a relatively straightforward hypothesis for a “complex” disease. The disease of atherosclerosis is complex in

biological terms; however, from the point of view of vascular mechanics, the disease is really “simple.” In mechanics, the failure of a pressure vessel occurs from fatigue in the region of stress-concentration. Similarly, we may expect that the failure of the artery (the pressure vessel) also occurs from fatigue in the region of stress-concentration. Furthermore, in case of nonbiological material, the failure presents itself as a rupture of the pressure vessel; however, in the case of the artery, we may expect failure to present itself as a pathological process. Thus, the hypothesis proposed is, *atherosclerosis is a result of failure of the artery from fatigue in the region of stress-concentration*. Now, we will expand on this concept so that atherosclerosis can be understood in terms of biology of the artery. For this, we need to recall the essential features of the artery and of atherosclerosis.

### 6.1. Essential Features

1. The artery has cyclic pressure, which produces cyclic stress in the artery wall.
2. The artery has branch ostia and bifurcation regions where stress-concentration occurs.
3. Cyclic load and region of stress-concentration are the two main requirements for fatigue failure.
4. Atherosclerotic plaques occur at branches and bifurcation and that, as proposed, represents fatigue failure of the artery (pressure vessel) there.
5. Atherosclerosis increases with mean pressure and pulse pressure just as fatigue failure increases (occurs sooner) with mean pressure and pulse pressure.
6. Atherosclerosis is inhibited by decreased transmural pressure, for example in the externally supported artery, which has less transmural pressure (less wall stress), just as fatigue failure is prevented by substantially reduced wall stress.
7. Atherosclerosis is reduced by reduced heart rate (as with  $\beta$ -blocker treatment) just as fatigue failure is reduced (delayed) with a reduced number of cycles imposed.
8. Atherosclerosis does not occur in the pulmonary artery and in the vein (unless substantially higher pressure is imposed) just as fatigue failure does not occur unless the stress is above a certain threshold value.
9. Atherosclerosis occurs at a pressure much lower than the bursting pressure of the artery, just as fatigue failure occurs at a stress much lower than the breaking stress of the material.
10. Atherosclerosis represents a process that produces a plaque, which grows with time just as fatigue represents a process where small damages accumulate over time to produce a failure.

Now, let us consider the cellular mechanism of atherosclerosis (fatigue failure).

### 6.2. Cellular Mechanism of Atherosclerosis

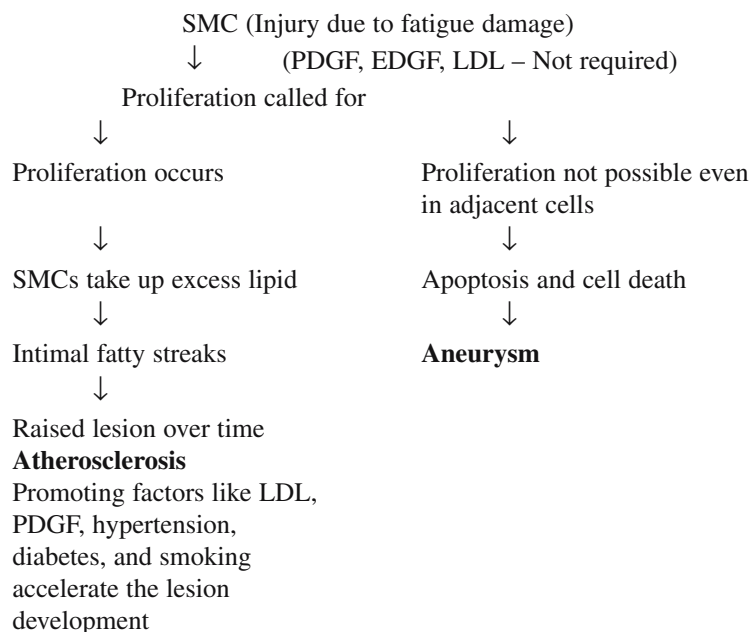
1. Stress in the wall of the artery, induced by pressure, is sustained primarily by the media (i.e., by smooth muscle cells and connective tissue).

2. Due to stress-concentration at the branches and bifurcations, there exist both higher pulsatile stress and higher pulsatile strain (stretch) in the media at these locations. Thus, SMCs are under higher cyclic tension and cyclic strain at these locations.
3. The wall stress is generally highest on the inner surface of the artery and decreases through the thickness toward the outside. Therefore, SMCs of the inner media are under the highest cyclic tension and cyclic strain.
4. Because of higher cyclic tension and cyclic strain, the SMCs of the inner media at the branches and bifurcations are easily “injured”; their cell-to-cell junction can be easily damaged and their cell-to-cell contact can be broken.
5. Injury to SMCs at these particular locations resulting from fatigue failure of the artery is the key to arterial disease including atherosclerosis.
6. SMCs are stimulated to proliferate both by cyclic strain and by removal of cell-to-cell contact inhibition.
7. The same forces produce changes in the endothelial cell morphology and in the connective tissue at these locations.
8. The same forces, through their influence on both the cells and the stretching of the tissue, promote increased penetration of LDL particles in this region.
9. LDL particles then serve as a promoting factor for SMC proliferation there.
10. Other factors that promote SMC proliferation at that location are hypertension, diabetes, cigarette smoking, and so forth.
11. Hence, SMCs located at the inner media, at the branches and bifurcations, become injured due to fatigue damage from pulsatile pressure, and this is the initial step in the disease of the artery.
12. When they proliferate due to injury stimulus, then atherosclerosis begins. This initial step does not require but can be aided by the presence of other agents like LDL.
13. The presence of a higher level of LDL, hypertension, diabetes, smoking, and so forth, is not required for the initiation or growth of atherosclerotic lesion; however, these factors can accelerate the disease process through enhancement of SMC proliferation.

## 7. Pathogenesis of Atherosclerosis and Aneurysm

Now, let us consider both atherosclerosis and aneurysm, the most common diseases of the artery. The basic premise used for the diseases of the artery is that all pressure vessels fail from fatigue in the region of stress-concentration. This premise was developed further to the point that fatigue failure presents itself as an injury to SMCs at the inner media in the branch and bifurcation regions. Obviously then, the injury to SMC could also result in cell death (apoptosis), which is the initial step in the development of aneurysms. Thus, we may express the unified mechanism of the arterial diseases as follows:

### 7.1. *Proposed Pathogenesis of Atherosclerosis and Aneurysm*



The main distinguishing feature of the proposed mechanism for atherosclerosis, from the previous mechanisms, is that the proposed mechanism does not require EDGF, PDGF, or LDL either for the initiation or for the growth of atherosclerotic lesion. It does not depend on the endothelial injury/dysfunction or lipid infiltration. The primary factor for both initiation and growth of the lesion is the same, and that is pulsatile pressure producing fatigue damage in the region of stress-concentration. It may be recalled that, in the artery, with each arriving pulse of pressure, the branch region stretches double the amount of the straight region (6% vs. 2.8%) (see Chapter 6). This differential stretching of SMC is the key event. It is important to remember also the arrangement of SMCs and connective tissue at the branch. In particular, not all of the SMCs are oriented in the same direction, and this imposes an additional challenge to the tissue when it has to stretch and even a bigger challenge when it has to stretch more. Through the thickness of the wall, when different layers of SMCs have different cell orientations, then the stretching of the wall imposes completely different forces on the cells, the forces that can only be more damaging to the cells (see Chapter 3). Furthermore, we have also noted that SMCs show a higher rate of cell replication at the branch in the normal artery, which would be expected in light of the challenges described above (see Chapter 9). According to the proposed mechanism, atherosclerotic lesions will begin and grow in all cases but perhaps at a slow rate. The presence of risk factors such as high level of cholesterol, high blood pressure, diabetes,

smoking, and so forth, increases the rate of SMC proliferation and thereby accelerates the disease process.

## 7.2. *Examples*

The above mechanism explains many observations described in this book and is illustrated by the following examples:

1. Why atherosclerotic plaques are most often eccentric? Because atherosclerosis begins on the side of the artery near the ostium or bifurcation.
2. How does one explain atherosclerosis in the straight segment of the artery, though an infrequent occurrence? Because there can be regions of small defects or weaknesses in the straight segment, and these regions then act like regions of high local stress and strain.
3. Why there is a close relationship between the two diseases (atherosclerosis and aneurysm), such as both occurring together in the abdominal aorta (see Chapter 15)? Because they share a similar mechanism for their genesis.
4. Why do intracranial aneurysms occur at the branch sites while extracranial arteries develop atherosclerosis at the branch sites?
5. Why in the intracranial arteries do aneurysms and atherosclerosis occur in close proximity to each other (see Chapter 14)?
6. Why do anastomotic aneurysms and anastomotic intimal hyperplasia occur at the same location (see Chapter 13)?
7. Why are many of the risk factors the same for both diseases?
8. Why do many of the drugs that protect against one disease also protect against the other?
9. This is the known mechanism of failure for nonbiological material.

We may also want to examine the stretch aspect of the coronary arteries in light of the proposed hypothesis. We know that coronary arteries are subjected to more cyclic stretch due to cardiac contraction than all other arteries. During the growth period, up to 20 years of age, atherosclerosis is not noted in any of the arteries except in coronaries. It could be speculated that the growth processes are able to mitigate the processes of atherosclerosis in all of the arteries except in coronaries, because the coronaries are subjected to more stretch than all others. The same reasoning suggests that atherosclerosis would occur more in coronaries than in other arteries.

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<http://www.springer.com/978-0-387-33816-3>

Vascular Mechanics and Pathology

Thubrikar, M.J.

2007, XXIII, 494 p., Hardcover

ISBN: 978-0-387-33816-3