Non-Invasive Measurement of Coronary Atherosclerosis

4.1 Pathophysiology of Coronary Atherosclerosis and Calcification

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4.1.1 Normal Artery Histology and Cell Function

In order to understand plaque formation and plaque composition it is necessary to have a knowledge of the normal histology. In general, arteries contain three concentric layers: the intima, media and adventitia (Fig. 4.1.1). The intima consists of a single layer of endothelial cells with only a small amount of underlying connective tissue. The intima is separated from the media by a thick layer of elastic fibers called the intern elastic lamina. The media is mostly composed of smooth muscle cells. Approximately the inner half of the smooth muscle cell layer receives its nutrients from the lumen via diffusion. The outer half, however, needs nourishment from blood vessels themselves, called the vasa vasorum, which course into the media from the adventitia. Between the media and the adventitia lies the external elastic lamina. The adventitia consists of connective tissue, nerve fibers and the vasa vasorum.

Based upon their location in the circulatory system, size, and functional microscopic anatomy, arteries can be divided into: large or elastic arteries (such as the aorta), medium sized or muscular arteries (such as the coronary arteries), small arteries with a diameter smaller than 2 mm, and arterioles. The thickness of the arterial wall gradually diminishes as the vessel becomes smaller, but its ratio to the lumen diameter becomes proportionally greater. Depending on their position and function in the arterial system, the basic configuration of the arterial walls, as described above, may vary, especially in the media and the extracellular matrix. For instance, the aorta needs to be able to expand during the systole. Therefore, the media is rich in elastic fibers and arranged in functional lamellae of smooth muscle cells and elastic fibers. In contrast, muscular arteries and arterioles regulate regional blood flow and blood pressure by changing luminal size by contraction or relaxation of the smooth muscle cells. In this part of the arterial system, the media contains cir-
cularly and spirally arranged smooth muscle cells, and the elastic fibers are limited to the internal and external elastic laminae.

The main cellular components of arteries are endothelial cells and smooth muscle cells. Endothelial cells form a continuous lining called the endothelium. The integrity of this single cell-thick layer is essential for the maintenance of vessel wall homeostasis and normal circulatory function. Endothelial cells have many different properties and functions, including: (1) permeability barrier function, (2) anticoagulant, antithrombotic and fibrinolytic effects, (3) extracellular matrix production, (4) oxidation of LDL, (5) regulation of inflammation and (6) regulation of cell growth. In addition to their contractile and relaxing properties, smooth muscle cells are able to synthesize collagen, elastin and proteoglycans and change (the function of) growth factors and cytokines.

4.1.2 Endothelial Dysfunction and the Pathogenesis of Atherosclerotic Plaques

Endothelial cells can respond to several stimuli by adjusting their normal physiological functions and by inducing new properties. This so-called endothelial activation can cause an increase in the expression of adhesion molecules and an increased production of growth factors and coagulation proteins. Endothelial dysfunction, however, can be responsible for the initiation of thrombus formation and atherosclerosis. Certain forms of endothelial dysfunction may develop within minutes and can be reversible, whereas others may require alterations in gene expression and protein synthesis, which may take days to develop.

Concerning the etiology of atherosclerosis, several major and minor clinical risk factors have been recognized. Well-established or major risk factors of atherosclerosis are cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus. In addition to these clinical risk factors, hemodynamic factors, in particular disturbed arterial flow and increased arterial pulsatile shear stress, also contribute to endothelial dysfunction. Moreover, patients with more than one risk factor will more often experience complications of atherosclerosis at a younger age than patients with only one risk factor. Hemodynamically disturbed arterial flow and pulsatile shear stress provide us with an explanation why atherosclerosis mainly arises at the level of bifurcations of the larger elastic arteries. Sites of predilection of atherosclerosis, in addition to coronary arteries, are the aorta, the carotid arteries and the femoral and popliteal arteries. According to the response to injury theory, endothelial dysfunction is thought to play a key role in the development of atherosclerosis. In dysfunctional endothelial cells increased abluminal transport of serum proteins occurs, in particular LDL-cholesterol. Upon oxidation in the intima of the arterial wall, LDL-cholesterol is phagocytosed by macrophages, which enter the intima as monocytes from peripheral blood. The initial stage of atherosclerosis, which may be observed already at young