1

Coronary artery disease pathophysiology: from basic principles to an interventional perspective

Alexandra C. Murphy, Ikaasa Suri, Roxana Mehran

Pathophysiology of atherosclerosis

The emergence of sophisticated techniques and technologies for the management of coronary artery disease (CAD) requires an understanding of the anatomic and histologic features of the coronary arteries and the diseases which affect them.

Histologic features of the normal coronary artery

Consistent with the basic organization of all human arteries, the coronary arterial wall is a tri-laminar structure with the outermost layer consisting of the adventitia, the middle layer consisting of the tunica media, and the innermost layer consisting of the tunica intima (Figure 1.1). The adventitia has a sparser population of cells than the other layers; specifically, it contains fibrous tissue made up of collagen and elastic fibers and is surrounded by vasa vasorum, nerves and lymphatic vessels. It is also a major site of immune surveillance and inflammatory cell trafficking and provides an important gateway for macrophage and leukocyte migration into the tunica intima of the artery wall.

Whereby the tunica adventitia is continuous with surrounding tissue, the underlying arterial layer of the tunica media consists of smooth muscle cells and connective tissue comprising elastic fibers, collagen and proteoglycans.[1] Smooth muscles cells are the spindle-shaped, nucleated powerhouse cells responsible for the contraction and dilation of the vasculature.[2] In large, coordinated assemblies

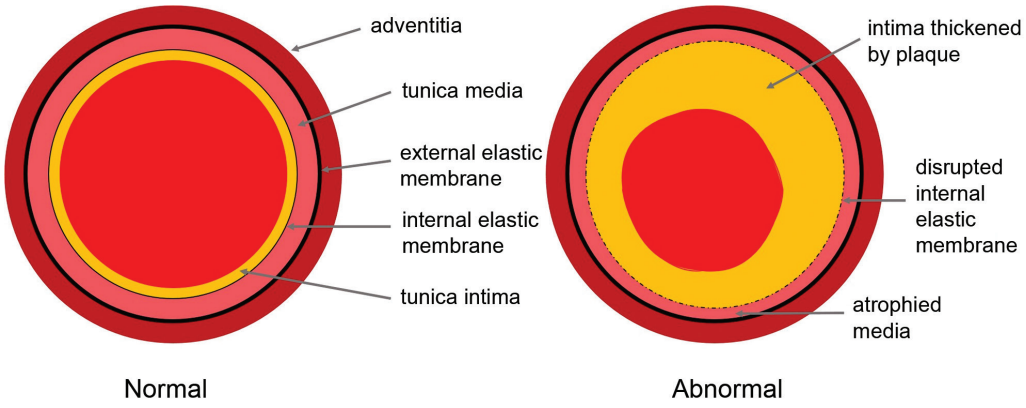

Figure 1.1 Histologic features of the normal *vs.* atherosclerotic coronary artery.

termed syncytia, they contract to change the size of the vessel lumen and control blood flow through arterial beds, typically at the level of the arteries and arterioles. Smooth muscle cells have the ability to proliferate and contribute largely to the extracellular matrix of the vessel. In larger arteries, abnormal smooth muscle contraction executed by these cells may cause vasospasm. The intima media underlying atherosclerotic plaque is considerably thinner than in normal vessels, and as smooth muscle cells die, the arterial wall undergoes ectatic remodeling, which can destabilize any existing plaque in that region of the vessel and ultimately contribute to aneurysm formation.[3] With aging, the tunica media also develops smooth muscle cells fibrillar collagens (types I and III), compounding the number of cells in that layer.

The most critical layer of the artery for the development of CAD is the tunica intima located on the basement membrane. This layer consists of a non-fibrillar collagen (type IV) and laminin. Endothelial cells, found predominantly within the arterial intima, maintain a contact surface with the blood and form the endothelium of the tunica intima.[4] Given the positioning of this layer, the endothelium contains molecules that maintain the blood in a liquid state. These molecules include heparin sulfate proteoglycan, which serves as a co-factor of antithrombin III, an inhibitor of thrombin, and thrombomodulin, which activates protein S and C to bind and inhibit thrombin. This is significant as thrombin inhibition will prevent thrombus formation on the endothelial surface, potentially protecting from myocardial ischemia and infarction.[5] Furthermore, the endothelial cells produce plasminogen activators including t-PA and u-Pa, which catalyze the formation of plasmin from plasminogen to breakdown thrombus.[6]

Below the endothelial layer of the tunica intima is the sub-endothelial layer that consists of smooth muscle cells and the extracellular matrix.[7] The extracellular matrix is rich in proteoglycan molecules and longitudinally oriented elastic

fibers. In a diseased state, proteoglycans play a significant role in trapping and retaining lipoproteins as cells accumulate in the intima during the pathophysiologic formation of atherosclerotic plaque.[8] As a result, normal coronary arteries will also resist the infiltration and accumulation of leukocytes triggered as an inflammatory response to lipoprotein buildup in the vessel walls.

The development of coronary atherosclerosis

The development of coronary atherosclerosis is a multifactorial interplay between genetic, environmental and metabolic influences.[9] Early atherosclerotic lesions, also known as "fatty streak" lesions, are precursors to the more clinically significant, advanced lesions that cause phenotypic CAD.[10] Early lesions consist of sub-endothelial accumulation of foam cells whereas advanced lesions consist of a buildup of lipoproteins and smooth muscle cells (Figure 1.2). When these lesions calcify, ulcerate, hemorrhage or thrombose in a process known as complicated plaque growth, an acute coronary occlusion resulting in myocardial ischemia or infarction can occur.[11] Alternatively, these lesions can grow to obstruct the lumen, without incurring rupture or erosion. This process is known as focal plaque growth, which leads to the development of luminal stenosis.[11]

Another process contributing to the development of coronary atherosclerosis is the hydrostatic alteration of blood flow in the coronary arteries caused by early lesions. These lesions locally disturb flow in the arteries and this disturbed flow

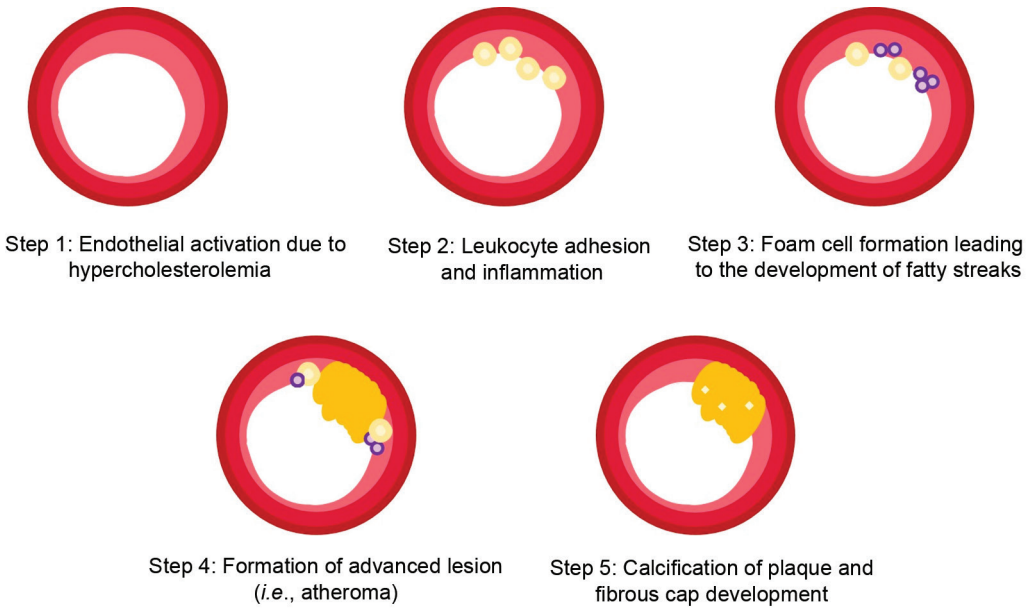

Figure 1.2 The development of coronary atherosclerosis.

further promotes atherosclerosis by inducing athero-protective mechanisms. In particular, the momentum transfer of the molecules within the blood augment the expression of genes that protect against atherosclerosis via the endothelial cells that have cilia and adhesion receptors that sense tension. These genes code for proteins such as superoxide dismutase, which catalyzes the formation of hydrogen peroxide to inhibit cell migration and hypertrophy, and nitric oxide synthase, which produces nitric oxide that prevents smooth muscle proliferation and leukocyte adhesion.[12, 13] Therefore, when laminar flow is replaced with turbulent flow in the vessels, the propensity for incipient atherosclerotic lesions increases because the protective signaling processes associated with laminar flow in the endothelial cells are turned off.[14]

The role of leukocytes and inflammation

Non-diseased arteries will typically resist the accumulation and adhesion of leukocytes. In contrast, in a hypercholesterolemic setting the endothelial production of superoxide anions is increased leading to the adherence of leukocytes and subsequent activation of the endothelium.[15] Once activated, the endothelium begins to express adhesion molecules that allow for the further accumulation of lipids and leukocytes, and LDL oxidation.[15] After adhering, the leukocytes penetrate the endothelial cell via transcytosis, allowing them to enter the intima. Further to this, specifically within the context of atherogenesis, VCAM-1 (CD106) on the surface of the endothelial cell interacts with the integrin protein VLA-4 expressed on monocytes and T lymphocytes to allow them to migrate through the intima.[16]

Once the atheroma is formed, P-selectins (CD62P) expressed on the endothelial cells overlying the plaque can adhere to selectins found on leukocytes. This interaction also helps in the migration of leukocytes across the intima by promoting saltation. At the same time, the existing macrophages are impaired from exiting the plaque due to retention factors including netrin-1.

The innate immune response plays a key role in the initial stages of plaque formation. Specifically, T cells local to the site of injury are activated and release cytokines to promote plaque formation.[17] The foam cells themselves are also a source of pro-inflammatory mediators and oxidant species. After the lesion begins to take form, dendritic cells, endothelial cells, and macrophages can present plaque antigens including lipoproteins, heat shock proteins, infectious agents, and B-glycoprotein Ib to T cells, which further secrete cytokines that modulate atherogenesis. Cytotoxic T cells promote the apoptosis of endothelial cells, smooth muscle cells and macrophages, all of which contribute to plaque progression. Class I helper T cells secrete IFN-gamma, lymphotoxin, CD40 ligand, and TNF-alpha, all of which activate the vascular walls to destabilize the forming plaques and heighten thrombogenicity. In particular, IFN-gamma recruits vascular smooth muscle cells to inhibit the synthesis of collagen in the atherosclerotic plaque, destabilizing the fibrous cap of the plaque and increasing its propensity

for hemorrhage.[18, 19] Class II helper T cells, on the other hand, have a less defined role in the development of atherosclerotic plaque.[18] One conventional hypothesis is that Th2 helper cells antagonize pro-atherogenic Th1 effects given its downstream downregulation of IFN-gamma.[18]

Lipid accumulation and foam cell formation

When lipoproteins accumulate in the vessels, they do so in the tunica intima and aggregate around proteoglycan molecules that typically maintain an antithrombotic state. This binding leads to increased susceptibility of the intima to chemical modifications, including oxidation, a process that is strongly associated with atherosclerosis development.[20] Oxidative stress can also be caused by the reduced expression of NADH and NADPH in vascular cells (*i.e.* endothelial cells, smooth muscle cells, fibroblasts, and infiltrating immune cells), lipoxygenases expressed by infiltrating leukocytes, or the enzyme myeloperoxidase. Other chemical modifications include those conducted by enzymes such as phospholipase A2, which hydrolyzes phospholipids to form free fatty acids.[21, 22] Lipoprotein accumulation, particularly at sites with higher LDL concentrations, also increases the permeability of the endothelial monolayer.

This chemical modification results in vascular insult and allows monocytes to migrate from the blood into the coronary tissue through the sub-endothelial space.[17] Here, the monocytes transform to macrophages. As additional lipoproteins aggregate, scavenger receptors on macrophages mediate the uptake of excessive lipids in the vessels. They do so by binding to the modified lipoproteins and assisting in their internalization. Once lipid-laden, these macrophages are termed foam cells. These cells possess the ability to replicate, with certain known growth factors assisting in their replication cycles. Together, groups of foam cells form the fatty streak, which is the first step in the formation of the atherosclerotic plaque and the precursor lesion to atheroma.

Smooth muscle, extracellular matrix, angiogenesis, and plaque mineralization

Both smooth muscle cells and the extracellular matrix play significant structural roles in atherogenesis. Smooth muscle cells in the atherosclerotic intima have increased levels of the embryonic isoform of smooth muscle myosin, allowing them to proliferate at relatively higher rates. These smooth muscle cells also contain more rough endoplasmic reticulum and fewer contractile fibers than normal smooth muscle cells.

Atherosclerotic plaques develop their own microcirculation. This phenomenon is attributed to the angiogenic peptides that are overexpressed in plaques including oncostatin M, P1GF, and VEGF. This microcirculation allows plaques to overcome nutrient-supply issues by increasing the traffic of leukocytes to the site. Ultimately, this allows for further smooth muscle cell proliferation and matrix

accumulation within the plaque, all of which increase its propensity for hemorrhage or thrombosis. Plaques also mineralize, a process known as vascular calcification.[23] This is especially important because calcification can alter the tensile forces on the plaque's cap, increasing the potential for plaque rupture.

Once the plaque burden exceeds the ability of the artery to remodel outwards, the plaque grows inwards and encroaches on the arterial lumen. Ultimately, this leads to luminal stenosis and impeded blood flow around the area of the plaque.

Coronary artery circulation

Coronary artery circulation can be broadly categorized into two groups: the epicardial coronary arteries and the microvasculature. The epicardial arteries originate at the base of the aorta and run along the outer surface of the heart.[24] Compared to the coronary microvasculature, the epicardial arteries maintain a relatively low resistance in a non-diseased state.

Anatomical considerations regarding vessel size, location, trajectory and coronary dominance are integral to the safety of percutaneous coronary intervention. Certain heterogeneity amongst patients must be considered. For example, the luminal diameter of the major coronary arteries is influenced by age, sex, coronary dominance and cardiac structure.[25] The visual assessment of luminal diameter at a given coronary anatomic location is integral to the quantitative assessment of the severity of CAD and must take into consideration these heterogeneities. In adults with a right dominant system, the mean luminal diameter of the left main coronary artery (LMCA) is 4 mm, the left anterior descending (LAD) artery is 3.6 mm, the left circumflex artery (LCx) is 3.0 mm and the right coronary artery (RCA) is 3.2 mm.[25] The left sided system generally tapers in diameter after extending from the left main bifurcation in the trajectory of the apex of the heart. In contrast, the right coronary artery is more constant in diameter until the origin of the posterior descending branch.[26]

Coronary dominance is determined by which coronary artery supplies the posterior descending artery (PDA).[27] The PDA supplies the inferior wall and the posterior third of the interventricular septum. In a right dominant state, the PDA originates from the RCA, while in left dominant hearts, occurring in up to 20% of patients, the PDA originates from the LCx. Co-dominance can occur whereby both the RCA and the LCx supply the PDA.[27]

Resistance to coronary blood flow plays a critical role in the complications of coronary artery disease. For example, under normal conditions, resistance across the epicardial arteries results in negligible conduit resistance. As a patient develops atherosclerosis, however, the narrowing of the epicardial artery becomes a dominant force, increasing the total coronary resistance and reducing the total resting flow. The microcirculatory vasculature, on the other hand, modulates changes in response to physical forces including shear stress and intraluminal pressure.

Alteration of coronary tone in response to changing metabolic demands is modulated by several factors including nitric oxide (NO), also known as endothelial-derived relaxing factor (EDRF), endothelium-dependent hyperpolarizing factor (EDHF), prostacyclin, and endothelin.[28-31] NO is produced by endothelial cells and in turn, activates the cGMP cascade within the cell. This process ultimately decreases intracellular calcium levels, allowing the vessel to relax.[28] Importantly, NO-mediated vasodilation of coronary arteries is impaired in patients who have established atherosclerosis because NO is deactivated by the superoxide anion generated within the plaque.[32] EDHF is also produced by the endothelium. Here, the signaling molecule hyperpolarizes smooth muscle by opening calcium-activated potassium channels, allowing vasodilation of the vessel.[29] In contrast, endothelin is a constricting factor that is mediated through transcriptional control.[31] Because of this, it enacts longer-term changes in coronary tone, a phenomenon that becomes increasingly important within the pathophysiologic context of atherosclerosis.

Ischemic mechanisms

Ischemia is defined as the imbalance between myocardial oxygen supply and demand and occurs when the myocardial oxygen demand outweighs the supply.[33] When this imbalance occurs, it can cause cardiac dysfunction, arrhythmias, myocardial infarction, and sudden death.

While the underlying concept of myocardial oxygen supply and demand mismatch remains the same across the different phenotypes of CAD, cardiac ischemia can be more specifically broken down into two groups: supply-induced ischemia and demand-induced ischemia. Supply-induced ischemia causes transmural ischemia, such as myocardial infarction, due to a transient coronary occlusion.[16] This may be due to coronary vasospasm, thrombosis or plaque rupture in a stenosed coronary artery. Demand-induced ischemia, in contrast, primarily affects the sub-endocardium due to the heart's inability to increase blood flow in response to increases in myocardial oxygen consumption.[16]

Supply-induced ischemia due to the disruption of the coronary circulation by atheroma results in a cessation of regional perfusion. The failure of oxygen delivery to the tissues causes an abrupt halt in aerobic metabolism. Once aerobic metabolism stops, creatine phosphate, used to transfer phosphate groups from ADP to ATP, is depleted. This reduction in the concentration of creatine phosphate in the cardiac cells pushes them to move towards anaerobic glycolysis. This process is less efficient in producing ATP, and subsequently the tissue ATP levels decrease, preventing necessary catabolic reactions from occurring. Tissue acidosis is triggered with the accumulation of catabolites in the cardiac cells causing an efflux of potassium into the extracellular space. This disruption in the cell's voltage potential ultimately results in myocyte death.

Other causes of myocardial ischemia trigger the same mechanistic cascade. They include thrombosis formation and plaque rupture, as well as vasospasm of the epicardial and microvascular coronary arteries.[33]

The initial phase of myocardial ischemia is reversible. Whereby, restoration of blood supply still allows both the structural and functional recovery of the damaged myocardial cells.[34] Irreversible ischemia occurs when ischemia evolves into myocardial infarction.[34] Myocardial infarction progresses from the sub-endocardium, furthest from the vasculature, to the sub-epicardium and is due to the transmural variation in collateral blood flow and tissue wall tension.[35] Similarly, the size of the infarct and areas at risk of ischemia are inversely related to collateral flow.

It is worth noting that a disruption of the endothelium is contributory but not entirely sufficient for myocyte death. Myocyte death also requires a pathophysiologic trigger, such as thrombus formation or sympathetic activation. For patients with coronary artery disease, ischemia is often caused by a focal vasospasm taking place due to a lack endothelium-dependent vasodilation responses. Specifically, as discussed earlier in this chapter, the endothelium of arteries with atherosclerosis have impaired NO production. In normal arteries, serotonin causes vasoconstriction which is typically mitigated by NO. However, in the diseased state, the reduced NO production allows for the direct effects of serotonin on the smooth muscle to predominate, constricting microcirculation and exacerbating myocardial ischemia.

After irreversible myocardial injury, the heart undergoes extensive remodeling that results in the accumulation of fibrous tissue across both infarcted and non-infarcted components.[36] This remodeling distorts the tissue structure, increasing its stiffness and limiting ventricular contraction.[36] These changes also result in a decrease in the maximum achievable flow in response to increased metabolic demands in the region of the infarct.[37]

Coronary microvascular dysfunction

The microvasculature is comprised of the coronary vessels with an internal diameter of less than 300 micrometers.[38] Their main role is to regulate the coupling between myocardial perfusion and myocardial demand for oxygen.[39] Short-term regulation of myocardial perfusion is achieved via adjustment of the vasculature diameter and typically results as a response to a change in metabolic demand, such as physical exertion. In contrast, chronic adjustment of the microvasculature is a result of structural modifications known as remodeling. This remodeling often occurs as a response to mechanical forces acting on the endothelium and smooth muscle cells of the microvasculature.[39]

For many patients with CAD, abnormalities in coronary microcirculatory control also contribute to epicardial coronary stenosis. Conversely, in the case of coronary microvascular dysfunction, patients may not have angiographically visible