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Coronary Atherosclerosis and Interventional Cardiology

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The atherosclerotic process in coronary arteries begins with endothelial dysfunction and may provoke thrombotic total occlusion and myocardial infarction. In this state-of-the-art review, we discuss recent evidence of atherosclerosis, vulnerable plaque, and hemodynamic changes in the coronary tree, as well as the current techniques we implement in the catheterization lab to evaluate coronary stenosis. It is clear that atherosclerosis is a chronic inflammatory condition with several consequences in the coronary tree, however, we are able now to characterize the plaque and to select the appropriate treatment for many patients. © 2015 IMSS. Published by Elsevier Inc.

Key Words: Coronary atherosclerosis, Vulnerable plaque, Interventional cardiology, Hemodynamics changes, Coronary stenosis.

Introduction

Atherosclerosis is a chronic inflammatory process that affects the arterial wall of the coronary arteries, carotids, aorta and peripheral vessels. The disease process is characterized by loss of elasticity of the arteries caused by an abnormal deposition of fibrous tissue and lipids throughout the intima that disrupts the architecture of the vessels and is manifested by partial or total obstruction of the flow with resulting ischemia (1,2).

Multiple factors contribute to the pathogenesis of atherosclerosis, including endothelial dysfunction, hyperlipidemia, hypertension, diabetes, smoking, immunological and inflammatory factors. Macrophages loaded with oxidized LDL particles release inflammatory substances, cytokines and growth factors such as monocyte chemotactic protein (MCP-1), intercellular adhesion molecules (ICAM-1), granulocyte and macrophage colony stimulating factors, soluble CD40 ligand, interleukins 1, 3, 6, 8 and 18, and tumor necrosis factor alpha (TNF-α) (3,4). These proinflammatory cytokines induce cell proliferation, contribute to the production of reactive oxygen species, stimulate matrix metalloproteinases and induce the expression of tissue factor, which promotes leukocyte activation and endothelial dysfunction, the initial step in atherosclerosis. Additionally, other molecules involved in the process of atherogenesis have been described such as lipoprotein-associated phospholipase A2 (Lp-PLA2), antioxidized LDL antibodies, angiotensin II, endothelin-1 and mitochondrial DNA damage (mtDNA) (5–7).

The histological stages of atherosclerosis include fatty streak, intermediate lesion, atheroma and thin capsule fibroatheroma. The process of atherosclerosis begins in childhood with the development of the fatty streak. The fatty streak is a focal intimal thickening with accumulation of lipid-laden macrophages (foam cells) and an extracellular matrix (8). Fibrous cap atheroma is defined as a plaque with well defined lipid core covered by a relatively acellular layer or by a fibrous layer composed of smooth muscle cells. The formation of both the intermediate lesion and the stable atheroma plaque is mediated by the gradual accumulation of connective tissue with an increase in the number of vascular smooth muscle cells (9). The thin layer fibroatheroma is composed of a necrotic lipid core with concomitant thinning of the fibrous layer, which poses an increase risk of rupture and exposure of the extracellular matrix. Once the extracellular matrix comes into contact with the blood stream, it activates mediators and promotes occlusive thrombus formation. Other clinical manifestations of atherosclerosis include aneurysm formation and blood flow-limiting stenosis (10).

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Biomechanical stress plays an important role in the development of cardiovascular diseases. Shear stress is one of the main components of biomechanical stress resulting from friction forces generated between blood and the vascular wall. Coronary artery shear stress regulates the release of vasoactive substances by the endothelium and influences the development and progression of atherosclerosis (11). Shear stress is the frictional force per unit area that blood flow exerts on the vascular wall. The main factors determining the viscosity are blood distribution and blood velocity (shear rate) (12).

In the coronary arterial tree, multiple tortuous segments and bifurcations lead to complex flow patterns. This heterogeneous distribution of shear stress in the coronary circulation produces regions of high and low shear stress. Low shear stress regions are more prone to the development of atherosclerosis, whereas high shear stress regions promote the formation of a protective environment against the process of atherosclerosis (Figure 1) (13,14).

In low shear stress regions, there are multiple changes that disrupt gene expression and metabolic pathways leading to endothelial dysfunction, expression of adhesion molecules and accumulation of pro-inflammatory lipids throughout the vessel wall. These findings have lead to the fact that atherosclerotic plaque originates mainly in the side wall of a coronary artery bifurcation, at the inner wall of a tortuous segment or immediately distal to a stenosis (15). Although shear stress cannot be directly measured within the coronary arteries due to their size and movement, there are now 3D computational models that are useful for studying the relationship between shear stress and the location and progression of atherosclerotic plaque (16).

The vulnerable atherosclerotic plaque often expresses a phenotype known as thin layer fibroatheroma, which poses an increased risk of rupture and thrombosis. As mentioned before, the vulnerable plaque is composed of a large necrotic core surrounded by a macrophage infiltrated thin fibrous layer (<65 microns), which separates the core from the vessel lumen (17). Even though atherosclerotic plaques may show positive remodeling, most cause progressive narrowing of the vessel lumen compromising the coronary blood flow. Rupture of the thin layer of the vulnerable plaque is responsible for most cases of acute myocardial infarction. This occurs when the mechanical stress of the fibrous layer exceeds that of the plaque (Figure 2). Arterial blood pressure is the main inducer of mechanical stress within the fibrous layer (wall stress). Shear stress magnitude is very low compared to that of the blood pressure and its influence on the mechanical stress of the fibrous layer is not significant. However, shear stress has a major role in endothelial function and atherosclerotic plaque composition, both of which are considered important factors in predicting the probability of plaque rupture (18,19).

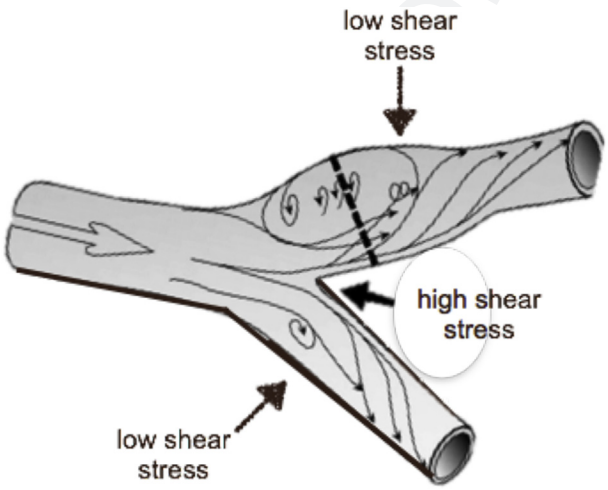

Figure 1. Shear stress forces in a coronary bifurcation. (A color figure can be found in the online version of this article.)

Once the capacity of eccentric remodeling has been exceeded, the atherosclerotic plaque produces progressive loss of the vessel lumen, which compromises blood flow leading to the development of signs and symptoms of myocardial ischemia. Most patients with atherosclerosis are asymptomatic until the lumen obstruction becomes >70% when blood flow becomes scarce during physical exertion. However, it has been shown that the majority of acute coronary syndromes occur as a result of rupture of the nonocclusive atheroma plaque, which obstructs the vessel lumen with newly formed thrombus. This vessel thrombosis is responsible for myocardial infarction; this process is called atherothrombosis (20).

The two main mechanisms responsible for atherothrombosis are plaque rupture and *in situ* endothelium erosion. Plaque rupture is the main mechanism of thrombosis and appears as a result of the imbalance between the forces exerted by blood flow on the fibrotic layer of the plaque and the rupture resistance of the fibrous cap itself. Inflammation has been proposed as the main predisposing factor occurring as a result of cytokine induction. T cells present in the subendothelium synthesize interferon gamma (INF-γ) and CD40-L. The former inhibits production of extracellular matrix by myofibroblasts, whereas the latter stimulates the production of types 1, 8 and 13 metalloproteinases by macrophages, which degrade fibrous cap fibrillar collagen. In conjunction with a high burden of necrotic-lipidic tissue, these make the plaque weaker and more prone to rupture. This is known as vulnerable plaque (21). Once the fibrous layer breaks, coagulation components within the bloodstream bind to tissue factor on the surface of macrophages. This union triggers the coagulation cascade and platelet aggregation with the result of thrombus formation. Multiple mechanisms such as endothelial cell apoptosis and degradation of the extracellular matrix have been proposed to explain the origin of atherothrombosis after plaque erosion. This type of thrombosis is more common in certain groups