The pathogenesis of atherosclerosis

Michael Mahmoudi

Abstract

Cardiovascular disease remains the world's leading cause of morbidity and mortality. The myriad of environmental risk factors and predisposing genes leads to a complex multifactorial disease process characterized by a fibro-proliferative and inflammatory process. This results in activation of cytokines, growth factors and vasoregulatory mechanisms, and leads to intimal thickening and ultimately luminal obstruction. Progressive luminal obstruction or acute rupture of the atherosclerotic lesion can lead to devastating complications such as myocardial infarction, stroke and death.

Keywords Atherogenesis; endothelial dysfunction; inflammation; MRCP; reactive oxygen species; statins

Key points

- Atherogenesis is a chronic inflammatory disorder characterized by endothelial dysfunction and the accumulation of a number of cellular components within the vascular intima
- Atherogenesis is enhanced by a number of risk factors, including hypercholesterolaemia, smoking, diabetes mellitus, hypertension and family history
- Atherogenesis can be modulated by statins

The pathogenesis of atherosclerosis

Atherosclerosis is a disease process characterized by the interaction between endothelial dysfunction, subendothelial inflammation and the 'wound healing response' of vascular smooth muscle cells (VSMCs). The atherosclerotic plaque is characterized by the accumulation of lipids, inflammatory cells, VSMCs and connective tissue within the arterial intima. The major cellular components of the atherosclerotic plaque are: VSMCs and lymphocytes, most abundant in the fibrous cap; macrophages, which dominate the lipid core; and platelets (Table 1). Atherogenesis should be viewed as a dynamic continuum of several stages, involving endothelial activation, lipid entry and modification, VSMC migration and persistent inflammation that ultimately leads to the formation of an atherosclerotic plaque (Figure 1).

Endothelial dysfunction

Vascular endothelial cells maintain the balance between vasodilatation and vasoconstriction, inhibition and stimulation of VSMC proliferation and migration, and thrombosis and fibrinolysis.[1] Endothelial dysfunction is recognized as one of the earliest precursors of atherogenesis and describes an imbalance between endothelial-dependent vasodilatation and endothelium-dependent contraction. One of the hallmarks of endothelial dysfunction is loss of normal endothelial-dependent vasodilatation.

Vasodilatation is predominantly achieved by nitric oxide (NO), as well as prostacyclin, bradykinin and endothelium-derived hyperpolarizing factors. NO, which is synthesized from L-arginine by the enzyme NO synthase and requires tetrahydrobiopterin as a co-factor, mediates its downstream function through the cyclic guanosine monophosphate (GMP) second messenger system. In addition to its vasodilatory action, NO mediates the inhibition of leucocyte adhesion to endothelial cells, maintenance of VSMCs in a non-proliferative state, and inhibition of platelet aggregation. Vasoconstriction is mediated predominantly by endothelin 1 and angiotensin II. Endothelin 1 also potentiates the action of other vasoconstrictors such as angiotensin II, noradrenaline (norepinephrine) and serotonin, as well as participating in leucocyte and platelet activation.

Numerous studies have demonstrated an association between conventional risk factors for atherosclerosis, such as hypertension, smoking, diabetes mellitus and hypercholesterolaemia, and endothelial dysfunction. There is also evidence supporting increased vascular production of superoxide species that react rapidly with NO leading to the production of peroxynitrite anions and loss of bioactivity of NO. The generation of such highly reactive oxygen species promotes oxidative degradation of tetrahydrobiopterin, leading to decreased production of NO.

Maintenance of inflammation and plaque progression

The decreased bioavailability of NO is accompanied by the expression of a spectrum of endothelial cell surface receptors such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1 and P-selectin, which bind platelets, monocytes and T lymphocytes. This initiates an inflammatory process that ultimately leads to the formation of an atherosclerotic plaque. The migration of these cells into the subendothelial space is facilitated by chemo-attractants such as monocyte chemo-attractant protein 1, oxidized low-density lipoprotein (LDL), macrophage colony-stimulating factor and a distinct family of T-cell chemo-attractants.

Platelets are one of the first cell types to arrive at sites of endothelial activation. The platelet surface receptors Ib and IIb/IIIa interact with ligands on the surface of endothelial cells and contribute to endothelial activation. Inhibition of such interaction in hypercholesterolaemic mice has been shown to reduce leucocyte infiltration and progression of atherosclerosis.

The entry of monocytes into the subendothelial space and their subsequent transformation into macrophages is a key step in atherogenesis. Once in the subendothelial space, the macrophages express the necessary scavenger receptors, for example

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Major cells implicated in atherogenesis

Key cells in atherosclerosis	Physiological role	Pathological role
Endothelial cells	Maintaining vascular tone, maintaining haemostasis	Endothelial dysfunction is a key first step in atherogenesis
Very smooth muscle cells	Maintaining vascular contractility	Formation of the fibrous cap; reduced numbers in regions of plaque rupture
Lymphocytes	Innate and adaptive immunity	Secretion of cytokines that contribute to the inflammatory response
Monocytes/macrophages	Innate and adaptive immunity	Formation of foam cells; contribute to the formation of the necrotic core
Platelets	Vascular thrombosis at sites of injury	Contribute to endothelial activation; key role in thrombosis acute coronary syndrome

Table 1

SR-A, CD-36 and LOX-1, to internalize modified lipoproteins. Internalization of these particles gives rise to lipid-laden macrophages, so-called foam cells. The macrophages also produce cytokines such as interleukin-1, tumour necrosis factor-α, transforming growth factor-β, proteolytic enzymes and growth factors such as insulin-like growth factor 1. These are critical in maintaining a chemotactic stimulus for adherent leucocytes, enhancing the expression of scavenger receptors and promoting macrophage replication.[2]

The entry of lymphocytes into the intima is mediated by vascular cell adhesion molecule 1. Once in the intima, T lymphocytes are activated in response to antigens such as oxidized LDL and begin to secrete a spectrum of cytokines that can interact with macrophages. CD40/CD40L interaction between the

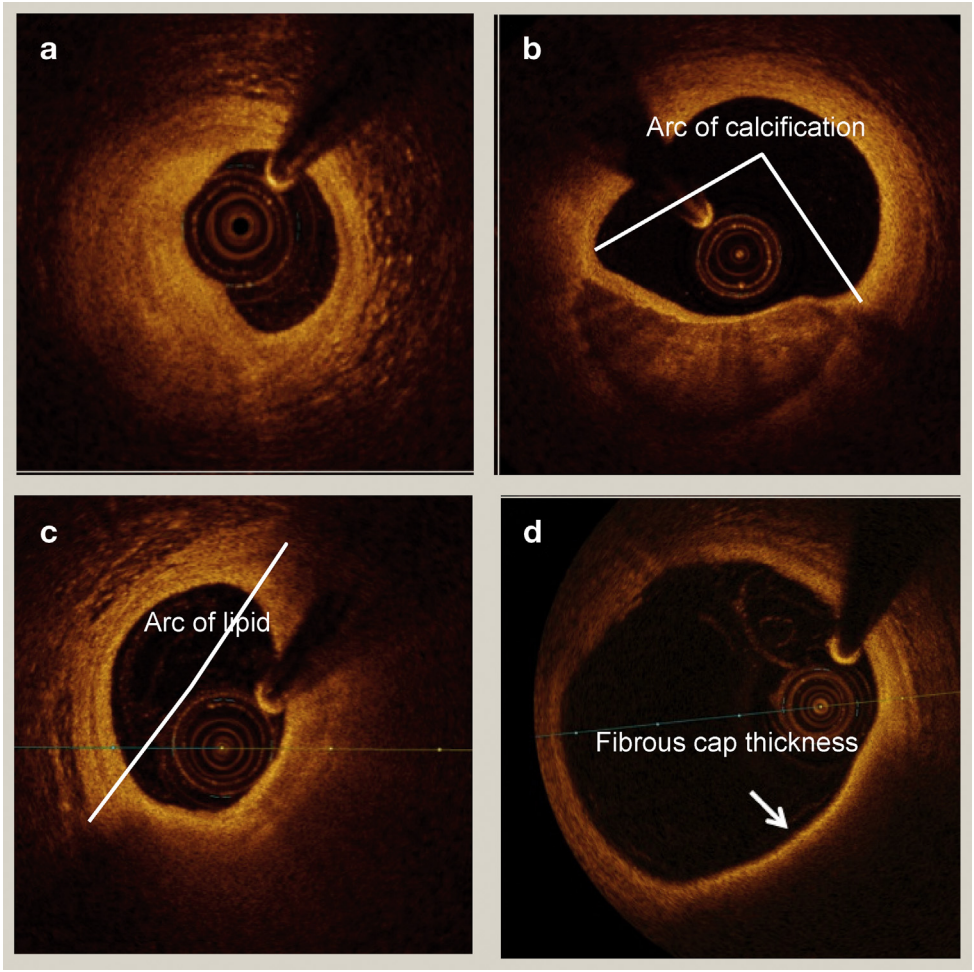

Figure 1 Examples of coronary atherosclerotic plaques. The plaques have been visualized by frequency domain optical coherent tomography: fibrotic (**a**), fibrocalcific (**b**), lipid-rich (**c**), and thin cap fibroatheromatous (**d**).

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