# SPECIAL ARTICLE
# The atherosclerotic plaque

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**Atherosclerosis is the most frequent cause of ischemic heart disease and cerebrovascular disorders. The condition is the leading cause of death in Western societies. At the core of this condition is the atherosclerotic plaque. It is within the structure of this lesion that multiple biochemical and cellular processes interact influencing its vulnerability to rupture and as a result acute ischemic events. This article will discuss the pathophysiology behind the atherosclerotic plaque, particularly those elements that lead to its instability and the medical tools currently available to counteract it.**

*Key words: Atherosclerosis, Lipids, Inflammation, Endothelium, Smooth muscle cell, Macrophages, Collagen, Vulnerable plaque, Matrix metalloproteinases, Wall stress, Thrombosis, Statins.*

Atherosclerosis is the most frequent cause of ischemic heart disease and the leading cause of death in Western societies. The occurrence of complicated thrombosis, usually due to the sudden rupture of the plaque surface, turns this generally benign disease into a malignant atherothrombotic event responsible of acute coronary syndromes such as unstable angina, myocardial infarction, and sudden death (1). As the name of this disease implies, plaques typically consist of two main components, an atheromatous gruel, which is lipid-rich and soft, and sclerotic tissue, which is collagen-rich and hard. This is the result of a process that starts early in life and usually takes decades to evolve into the mature plaques.

## The atherosclerotic plaque

The process responsible for the formation of the atherosclerotic plaque starts with the accumulation of lipoprotein particles (LDL) in the intima; these lipoproteins undergo modifications that include oxidation and glycation. Oxidative stress, including products found in modified lipoproteins, can induce local cytokine generation. The cytokines induce increased expression of adhesion molecules for leukocytes that cause their attachment and chemo-attractant molecules that direct their migration into the intima. Blood monocytes, entering the artery wall in response to chemo-attractant cytokines, such as monocyte chemo-attractant protein 1, encounter stimuli such as macrophage colony stimulating factor that can augment the expression of scavenger receptors. Scavenger receptors mediate the uptake of modified lipoprotein particles and promote the development of foam cells. Macrophage foam cells are a source of mediators, including other cytokines and effector molecules, such as hypochlorus acid, superoxide anion, and matrix metalloproteinases. Smooth muscle cells in the intima divide, and other smooth muscle cells migrate into the intima from the media. Smooth muscle cells can then divide and elaborate extracellular matrix, promoting extracellular matrix accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak can evolve into a fibro-fatty lesion. In later stages, calcification can occur and fibrosis continues, sometimes accompanied by smooth muscle cell death, including apoptosis, yielding a relatively acellular fibrous capsule surrounding a lipid-rich core that may also contain dying or dead cells and their debris (2). Proliferation of smooth muscle cells, matrix synthesis and lipid accumulation may narrow the arterial lumen gradually and lead to myocardial ischemia and anginal pain, but survival is good if thrombotic complications can be prevented. As a result, the crucial question is why some plaques remain thrombus-resistant and innocuous while others, after years of indolent growth, become thrombus-prone and life-threatening. In this light, plaque vulnerability and thrombogenicity have emerged as being more important than plaque size and stenosis severity.

## The vulnerable plaque

For many years, the likely culprit in acute coronary syndromes was thought to be the severity stenotic lesion. It

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has been realized, however, that it is often the more modest stenosis that is the actual substrate for acute events. When considering the vulnerability of a plaque to rupture, the focus should be on its composition rather than size and stenosis severity. The three major determinants of a plaque vulnerability to rupture are: the size and consistency of the lipid-rich core, the thickness and density of smooth muscle cells and collagen content of the fibrous cap overlying the core, and active inflammatory and immunological processes within the fibrous cap characterized by an increased density of macrophages, T lymphocytes, and mast cells (1). Cap "fatigue" may also play a role, as long-term repetitive cyclic stresses can weaken the material and increase its vulnerability to fracture, leading to sudden and unprovoked mechanical failure and disruption (3).

The size of the atheromatous core is vital for the stability of individual plaques. Studies conducted on aortic plaques have shown that plaques containing a core occupying more than 40% of the plaque area are considered particularly vulnerable and at high risk of rupture and thrombosis (4). The consistency of the core, an important aspect of plaque stability, depends on temperature and lipid composition. The core gruel has a toothpaste consistency at room temperature postmortem and is softer at body temperature in vivo. Liquid cholesteryl esters soften the gruel, while crystalline cholesterol has the opposite effect. In view of this, therapies that lower lipids are expected to deplete plaque lipid with an overall reduction in liquid and mobile cholesteryl esters, and an increase in the solid and inert crystalline cholesterol, which should result in a stiffer and more stable plaque (3).

The thickness, cellularity, matrix, strength and stiffness of fibrous caps vary widely. Cap thinning and reduced collagen content increase a plaque's vulnerability to rupture. Caps of eccentric plaques are often thinner and most heavily foam cell infiltrated at their shoulder regions where they most frequently rupture. Collagen is important for the tensile strength of tissues, and ruptured aortic caps contain fewer smooth muscle cells and less collagen than intact caps (5). This lack of smooth muscle cells could lead to plaque desestabilization, disruption and thrombosis.

Disrupted fibrous caps are usually heavily infiltrated by macrophage foam cells and such rupture-related macrophages are activated, indicating ongoing inflammation at the site of plaque disruption. In eccentric plaques, the shoulder regions are common sites for both active inflammation and disruption, foam cell infiltration weakens caps locally, reducing their tensile strength. Studies have shown that culprit lesions responsible for the acute coronary syndrome contain significantly more macrophages than lesions responsible for stable angina pectoris (6). Macrophages are capable of degrading extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and a family of matrix metalloproteinases (collagenases, gelatinases and stromeolysins) which may weaken the fibrous cap, predisposing it to rupture. The matrix metalloproteinases are secreted in a latent zymogen form requiring extracellular activation, after which they are capable of degrading virtually all components of the extracellular matrix. Collagen is the main component of caps responsible for their tensile strength. It has being shown that human monocyte-derived macrophages are capable of degrading collagen of aortic fibrous caps. Besides macrophages, a wide variety of cells may produce matrix metalloproteinases. Activated mast cells may secrete powerful proteolytic enzymes that can activate pro-matrix metalloproteinases secreted by other cells. Mast cells are actually present in shoulder regions of mature plaques and at sites of disruption, but at very low density. Neutrophils are also capable of destroying tissue by secreting proteolytic enzymes, but they are rarely found in intact plaques. Neutrophils may occasionally be found in disrupted plaques beneath coronary thrombi, probably entering these plaques shortly after disruption. They may also migrate into the arterial wall shortly after reperfusion of occluded arteries in response to ischemia or reperfusion (7).

Studies have shown over-expression of the potent immune mediator CD40 and its counterpart CD40 ligand in experimental and human atherosclerotic lesions. Ligation of CD40 on atheroma-associated cell types, such as endothelial cells, smooth muscle cells and macrophages, mediates functions that are important to the atherogenesis process, such as the expression of cytokines, chemokines, growth factors, matrix metalloproteinases, and procoagulants (8). On the other hand, other studies have targeted neovasculature as an important factor contributing to atherosclerotic plaque vulnerability. Intimal neovasculature arising from the adventitial vasa vasorum has been associated with inflammatory infiltrates. Neovasculature has an important role in the recruitment of leukocytes to the shoulder regions of lipid-rich plaques (9). Once these cells reach these areas of the plaque, they start a series of biochemical processes that lead to tissue destruction, rupture of the elastic lamina, and finally of the cap, which will cause plaque disruption followed by luminal thrombosis responsible of the acute coronary syndrome.

The risk of plaque disruption is related to both intrinsic and structural plaque features as well as to extrinsic stresses imposed on the plaque. When a material is exposed to a steady load that does not cause immediate

fracture, the material may weaken if the load is applied repeatedly. Ultimately, this repetitive stress may lead to sudden fracture of the tissue due to fatigue. Cyclic stretching, compression, bending, flexion, shear and pressure fluctuations may fatigue and weaken a fibrous cap, causing spontaneous rupture. If fatigue plays a role, lowering the frequency (heart rate) and magnitude (flow-and-pressure- related) of loading should reduce the risk of plaque disruption (3). Some of the most important elements that may represent extrinsic stresses imposed on plaques are: blood pressure, pulse pressure, heart contraction, spasm, capillary plaque bleeding, and fluid dynamic stress.

The luminal pressure induces both circumferential tension and radial compression of the vessel wall. The circumferential wall tension caused by blood pressure is given by Laplace´s law, which relates luminal pressure and radius to wall tension. The higher the blood pressure and the larger the luminal diameter, the more tension will develop in the wall (10). If components within the wall, like the soft gruel, are unable to bear the imposed load, the stress is redistributed to adjacent structures, such as the fibrous cap over gruel, where it may critically concentrate. The consistency of the gruel may be important for stress distribution within plaques; the stiffer the gruel, the more stress it can bear and correspondingly less is redistributed to the adjacent fibrous cap. Calcification may also play a role in making the plaque more stable. The thickness of the fibrous cap is most critical for the peak circumferential stress; the thinner the fibrous cap, the higher the stress that develops in it. For fibrous caps of the same tensile strength, caps covering mildly or moderately stenotic plaques are probably more prone to rupture than caps covering stenotic plaques, because the former have to bear a greater circumferential tension (11).

In terms of the pulse pressure, the propagating pulse wave causes cyclic changes in lumen size and shape with deformation and bending of plaques. Eccentric plaques typically bend at their edges, at the junction between the stiff plaque and the more compliant plaque-free vessel wall (12). Changes in vascular tone also cause bending of eccentric plaques at their edges. Cyclic bending may, in the long term, weaken these points leading to unprovoked "spontaneous" fatigue disruption, while a sudden accentuated bending may trigger rupture of a weakened cap.

Regarding heart contraction, the coronary arteries are tethered to the surface of the beating heart and they undergo cyclic longitudinal deformations by axial bending (flexion) and stretching, especially of the left anterior descending coronary artery. Like circumferential bending, a sudden accentuated longitudinal flexion may trigger plaque disruption, while long term cyclic flexion may fatigue and weaken the plaque.

Concerning spasm, plaque rupture and vasospasm do frequently coexist, but rupture most likely gives rise to spasm rather than vice-versa (13). Onset of myocardial infarction is uncommon during or shortly after drug-induced spasm of even severely diseased coronary arteries indicating that spasm infrequently precipitates plaque disruption and luminal thrombosis (14).

In terms of capillary plaque bleeding, bleeding and transudation into plaques from thin-walled new vessels originating from vasa vasorum, frequently found at the plaque base, could theoretically increase the intraplaque pressure with resultant cap rupture from the inside (15).

Finally, regarding fluid dynamic stress, high blood velocity within stenotic lesions may shear the endothelium away, but whether high wall shear stress alone may disrupt a stenotic plaque is questionable (16). The absolute stresses induced by wall shear are usually much smaller than the mechanical stresses imposed by blood and pulse pressures, but are not directly comparable, as the wall shear stresses act tangentially to the endothelium while blood and pulse pressures act radially and circumferentially on the plaque surface.

In addition to structurally vulnerable plaques that may precede plaque instability and eventual disruption, functionally vulnerable plaques may also exist. Thrombosed plaques without detectable fissures represent a substantial percentage of culprit lesions found post-mortem, yet they must have been thrombogenic enough to lead to an acute coronary syndrome. Their vulnerability is most likely caused by a thrombogenic or high-risk blood and/or local pro-inflammatory cytokines that promote thrombosis, sometimes also in the absence of intraplaque inflammatory cell infiltrates and in the absence of a lipid core (17). In patients with multiple fissured plaques and/or thrombi with layers of different ages, the possibility of a widespread waxing and waning of coronary inflammation and of systemic blood thrombogenicity should be considered, which may or may not be superimposed on a baseline structural vulnerability. The association of multiple inflamed plaques or of widespread endothelial activation and elevated systemic inflammatory markers in some patients with acute coronary syndrome suggests there may be isolated or multiple inflamed vulnerable plaques or a vulnerable endothelium. Also, some inflamed plaques can remain vulnerable for a period of weeks and months, and could be identified by persistent elevation of systemic inflammatory markers, such as C-reactive protein. In patients showing such inflammation, it may be difficult to identify which coronary plaque may suddenly flare up and become unstable, particularly if such event

may occur also in the absence of inflammatory cell infiltrates and of a central lipid pool (18).

**The management of the vulnerable plaque**

The goal in the management of the vulnerable plaque is to achieve a regression of the atherosclerotic lesion to the point in which it becomes stable, and as a result, not prone to disruption which may lead to thrombosis. This objective is attended by taking into consideration the components of the structurally vulnerable plaque with its intrinsic and extrinsic factors, previously discussed, as well as the components of the functionally vulnerable plaque. In the past several years, a series of drugs with different properties have being developed, which are the current medical tools available to deal with this disease. In the same manner, multiple studies are currently underway evaluating other substances which my have the potential in the near future to join the actual armamentarium against the atherosclerotic plaque.

One of these substances is the agonist of the peroxisome proliferator-activated receptors (PPAR). The PPAR family is comprised of three different proteins: PPARα, PPARβ and PPARγ. Natural ligands for these receptors include fatty acids and oxidized fatty acids. The relevance of PPAR pathways to metabolic disease is underscored by the use of the fibrates (PPARα agonists) and the thiazolidinediones (PPARγ agonists) to treat hyperlipidemia and type II diabetes mellitus, respectively. The expression of PPARs in cells of the arterial wall has prompted a number of investigations into the effects of PPAR agonists on atherosclerosis. It has been shown that activation of each of the PPARs with selective agonists inhibits the expression of inflammatory markers in the artery wall (19). Also, those PPAR activators inhibit inflammatory gene expression in cultured macrophages (20). Specifically, it was found that PPARγ agonists reduce the expression of inflammatory mediators (21). It has also being found that PPARα and γ ligands inhibit macrophage foam-cell formation (22). PPARγ ligands reduce cholesterol esterification in macrophages. They also increase cholesterol efflux from macrophages to HDL. In short, PPAR agonists are likely to exert anti-atherosclerotic properties by multiple mechanisms including improving systemic lipid levels, improving insulin resistance, inhibiting the accumulation of macrophage foam cells, and reducing the expression of inflammatory mediators.

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors exert many pleiotropic effects on the vascular wall. These include beneficial effects in endothelial function and blood flow, decreasing LDL oxidation, enhancing the stability of atherosclerotic plaques, inhibiting vascular smooth muscle cells proliferation and platelet aggregation, and reducing vascular inflammation (23). Furthermore, studies have suggested that statins may depress vascular contraction by reducing cytosolic calcium release in vascular smooth muscle cells and also, that they appear to exert competitive and non-competitive type antagonisms on noradrenaline action (24). As a result, decreasing vascular contraction will reduce regional wall stress on the atherosclerotic plaque making it more stable and less prone to rupture.

Beta blockers also play an important role in the management of atherosclerotic plaques. By lowering the frequency and magnitude of loading towards the fibrous cap, the possibility of cap fatigue is less and the risk of plaque disruption is reduced. This is achieved by the reduction in heart rate and blood pressure. This could explain the beneficial effect of these drugs after myocardial infarctions, reducing the incidence of reinfarction (25).

Studies have shown that angiotensin converting enzyme inhibitors (ACE-I) reduce atherosclerosis. This is probably related to the suppression of the mitogenic and potent vasoconstrictor angiotensin II (A-II). By reducing vasoconstriction, less regional wall stress is exerted upon the fibrous cap reducing the risk of plaque rupture. Also by reducing the production of A-II, the stimulus for proliferation of endothelial and smooth muscle cells on the vascular wall that may contribute to plaque formation is also reduced. Similar results have been seen in studies with angiotensin II receptor blockers.

Other important agents in the management of atherosclerotic plaques that help in the prevention of acute ischemic events are those that have an antiplatelet effect. Their role is to interfere with platelet activation and aggregation and as a result, in thrombus formation. Different drugs interfere with different pathways of platelet activation. Aspirin interferes with the pathway dependent on thromboxane A2. Clopidogrel interferes with the pathway dependent on ADP. Tirofiban, eptifibatide and abciximab inhibit the glycoprotein IIb-IIIa receptor, blocking the final common pathway to platelet aggregation. The latter agents are used not from a preventive standpoint, but in the scenario of an acute coronary syndrome that will require an invasive strategy.

Moreover, there have been attempts to develop agents that may also interfere with specific clotting factors in the coagulation system with the objective of blocking the formation of fibrin, and as a result, of the occlusive clot. In the future, drugs that could directly block factor Xa and thrombin successfully, without major side effects, may probably be developed. Agents that inhibit tissue factor, the main initiator of blood coagulation, are also being developed in an attempt to design new antithrombotic strategies. In the mean time, heparin, particularly the low

molecular weight type, is being used to prevent fibrin formation specifically in the setting of an acute coronary syndrome.

Regarding tissue factor, studies have demonstrated that it is not only involved in blood coagulation, but also in cellular migration and angiogenesis (26). It is expressed strongly in lipid-rich plaques and released from the content of apoptotic cells in the atheromatous lesion. According to this, a low lipid diet attempts to decrease tissue factor in the plaque (reducing the thrombotic potential of a ruptured plaque) and block the apoptotic process itself. Research is being done in this area with the purpose of developing other therapeutic strategies in the future which may help reduce thrombus formation from the unstable plaque.

Finally, in the context of patients at high risk of developing atherosclerotic disease, such as those with diabetes, dyslipidemia or hypertension, early preventive measures are critical. Lifestyle modifications including beginning exercise programs, lipid lowering diets, smoking cessation and good compliance with medical treatment is of utmost importance. Achieving goals such as keeping a systolic blood pressure no higher than 120 mmHg, or an LDL lower than 100 mg/dL (an ideal value of 70 mg/dL) or glycosylated hemoglobin of 6 or less in diabetics are important steps toward prevention of this disease.

As we have seen, the management of the vulnerable plaque includes a variety of agents with multiple mechanisms of action. Its fundamental purpose is to modify or stabilize the plaque to avoid rupture that may cause acute ischemic events. Nowadays, there is technology that promises to be a very important tool in monitoring the effects of therapeutic interventions on plaque composition. An imaging modality known as serial non-invasive magnetic resonance imaging (MRI), which was started to be used a few years ago as a method of quantifying atherosclerotic plaque composition, can potentially allow not only the identification of these vulnerable atherosclerotic lesions, but also monitor the effects of therapeutic interventions for stabilization of the plaque composition. Studies have shown that serial noninvasive MRI can monitor changes in atherosclerotic plaques composition under conditions of atherosclerotic progression and regression (27).

## Conclusion

Atherosclerosis is a systemic disease involving the vascular wall that starts early in life, but takes decades to evolve the mature plaques responsible for acute ischemic events. Atherosclerotic plaques are structures that far from being inanimate areas of a vessel are very dynamic tissues where multiple biochemical and cellular processes take place. These processes eventually lead to the vulnerable plaque which, influenced by several factors, will lead to rupture and atherothrombosis. Such events may result fatal and are responsible of making it the leading cause of death in the Western world. In response to this disease, multiple agents working through diverse mechanisms are been used today. Although there is greater understanding of this disease, still many aspects are waiting to be discovered and more innovative therapeutic strategies are promising in the future.

## Resumen

La ateroesclerosis es la causa más frecuente de enfermedad isquémica del corazón y cerebrovascular, por ende, la causa más común de muerte en el mundo occidental. La raíz de esta condición es la placa ateroesclerótica. Es dentro de la estructura de esta lesión que se entrelazan múltiples procesos bioquímicos y celulares influenciando la vulnerabilidad de la placa que resulta en su ruptura y causa la aterotrombosis responsable de eventos isquémicos agudos. En este artículo, se discute la patofisiología detrás de la placa ateroesclerótica, particularmente aquellos elementos que llevan a su inestabilidad. También se discuten las herramientas médicas disponibles al momento para contrarrestar los efectos nocivos de este padecimiento.

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