Acute thrombosis, which frequently complicates the evolution of atherosclerosis, leads to cardiovascular, cerebrovascular and peripheral events. Thrombosis occurs over plaques because of a disruption or tear in the cap of a lipid-rich plaque that leads to exposure of blood to highly thrombogenic plaque components because of denudation and erosion of the endothelial surface. Therefore, the crucial question is why atherosclerosis suddenly becomes complicated by life-threatening thrombosis. Plaque stabilization could be a crucial therapeutic intervention to combat the harmful consequences of coronary atherosclerosis through agents that can favourably impact on plaque pathobiology. (Eur Heart J Supplements 2002; 4 (Suppl B): B22–B27) © 2002 The European Society of Cardiology

**Key Words:** Atherosclerosis, passivation, plaque.

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**Introduction**

Coronary atherosclerosis is by far the most frequent cause of ischaemic heart disease. Plaque disruption with superimposed thrombosis is the main cause of acute coronary syndromes, including unstable angina, myocardial infarction and sudden death. Therefore, to achieve event-free survival, the crucial question is not why atherosclerosis develops but rather why, after years of indolent growth, it suddenly becomes complicated by life-threatening thrombosis.

The unifying pathophysiological concept of atherothrombosis identifies the coexistence of atherosclerosis in several vascular districts and the formation of a superimposed thrombus, which lead to the clinical pictures of ischaemic heart disease, cerebrovascular disease and peripheral obstructive arterial disease. The initially silent progression of arterial plaque, prompted by classic atherosclerosis risk factors such as cigarette smoking, hypertension, diabetes mellitus and dyslipidaemia, is followed by a phase of acute or chronic progression toward an increasing degree of stenosis caused by thrombosis. In this phase, haemostasis-related risk factors (i.e. factor VII, fibrinogen, plasminogen activator inhibitor-1) and platelets play a crucial role. The American Heart Association divided the sequence of steps that characterize plaque evolution into six stages (Table 1).

Plaque disruption and/or endothelial activation represents the main trigger for coronary events, through exposure of plaque thrombogenic components to platelets and to clotting components of flowing blood. Therefore, the primary mechanism that leads to both mural and occlusive thrombosis is represented by the adhesion and aggregation of platelets in disrupted plaques and by fibrin formation, with consequent strengthening of platelet thrombi.

**Atherosclerosis and atherothrombosis**

Atherosclerosis involves the following pathological processes: inflammation, with endothelial activation and monocyte recruitment; smooth muscle cell proliferation and migration, and matrix synthesis; lipid accumulation; necrosis, possibly related to the cytotoxic effect of oxidized lipid; and calcification, which may represent an active rather than a dystrophic process. Thrombosis represents the final crucial mechanism, with platelet recruitment and fibrin formation, and is thus considered a complication rather than a component of atherosclerosis. Worthy of note is that coronary occlusion and myocardial infarction frequently take place in the presence of mild or moderate stenosis; the smallest plaques may also lead to acute coronary events in the event of abrupt occlusion because they are less frequently associated with protective...
collateral circulation. Furthermore, small plaques may be dangerous because of their number.\[18–20\].

Thrombosis over plaque may occur via two mechanisms. The first is characterized by endothelial erosion; in this case a thrombus is formed on the surface of the plaque. The second is characterized by disruption or tear in the cap of a lipid-rich plaque; in this case, intra-plaque thrombosis takes place, which may or may not be followed by thrombosis of the lumen. Among the factors that precipitate major thrombi, plaque disruption has been reported to be more common, by a ratio of 3 : 1, than the process of endothelial denudation.\[2\]. However, the ratio is reduced to 1-3 : 1 in relatively young persons.\[3\].

### Thrombosis due to endothelial erosion

Thrombi due to endothelial erosion often occur at sites of pre-existing high-grade stenosis. This form of thrombosis is due to the exposure of collagen and tissue factor (a potent thrombogenic protein) to flowing blood as a result of endothelial denudation. Indeed, once plaques have reached an advanced stage (American Heart Association types IV and V), some focal platelet deposition is almost ubiquitous.\[4,5\]. Such microscopic platelet thrombi have no clinical significance other than perhaps to stimulate smooth muscle growth. These very small focal areas of loss of endothelial cells may be a stimulus for endothelial regeneration, but with the implication that the function of the new endothelial cells may be abnormal and may predispose to vasoconstriction.

Larger areas of denudation of endothelial cells cause larger thrombi that contain large amounts of fibrin and red cells in addition to platelets, and can cause lumen obstruction to a sufficient degree to cause symptoms.\[3,21\]. This form of endothelial loss and erosion has been associated with marked accumulation of activated lipid-filled macrophages beneath the endothelium, an increase in T-lymphocytes, and expression of major histocompatibility complex type II antigens by adjacent smooth muscle cells.\[22\]. These findings suggest that the endothelial disruption is associated with inflammatory activity. It has been shown\[3\], however, that plaques that are rich in smooth muscle cells and proteoglycans but which are relatively poor in lipids, macrophages and inflammatory cells can also develop endothelial erosion and undergo thrombosis, particularly in women.

### Thrombosis due to plaque disruption

Plaques that contain a soft atheromatous core are unstable and prone to rupture, following which highly thrombogenic components are exposed to flowing blood. Such disrupted plaques underlie approximately 75% of the thrombi responsible for acute coronary syndromes.\[23–26\]. Unlike thrombi caused by endothelial erosion, those that are generated by plaque disruption occur at sites with a lower degree of initial stenosis. The risk of plaque disruption is related to the vulnerability of individual plaques and to extrinsic dynamic forces that act on the plaques. Patho-anatomical examination of intact and disrupted plaques and in vitro mechanical testing of isolated fibrous caps from aorta indicate that vulnerability to rupture depends on the following: size and consistency of the atheromatous core; thickness and collagen content of the fibrous cap covering the core; inflammation within the cap; and cap ‘fatigue’.

### Atheromatous core

Although the average stenotic coronary plaque contains fibrous tissue that is much harder than the soft atheromatous contents of the plaque, a significant atheromatous component is usually present in culprit lesions.\[2\]. Gertz and Roberts found much larger atheromatous cores in 39 segments with plaque disruption than in 229 segments with an intact surface (32% and 5–12% of the plaque area, respectively). In aortic plaques, Davies et al.\[28\] identified a critical threshold; intact aortic plaques containing a core occupying more than 40% of the plaque were considered at
high risk for rupture and thrombosis. The atheromatous core is rich in lipids and it usually is soft at body temperature in vivo\textsuperscript{[20]}.

**Cap thickness**

Fibrous caps vary widely in thickness and cellularity, but they are often thinnest (and macrophage infiltrated) at their shoulder regions, where disruption most frequently takes place\textsuperscript{[23]}. Disrupted aortic caps contain fewer smooth muscle cells (the collagen-synthesizing cell in plaques) and less collagen than do intact caps\textsuperscript{[29]}. Loss of cells and calcification in fibrous caps are associated with increased stiffness\textsuperscript{[30]}, but the significance of cap stiffness for susceptibility to rupture is unknown.

**Inflammation (and infection)**

Histopathological data have led to the concept that inflammation plays a key role in the cascade of events that eventually result in plaque erosion and fissuring\textsuperscript{[22,31,32]}. Van der Wal et al.\textsuperscript{[22]} identified superficial macrophage infiltration in plaques beneath all of the 20 coronary thrombi examined. Whether the underlying plaque was disrupted or just eroded, the macrophages and adjacent T lymphocytes were activated (as assessed using immunohistochemical techniques), indicating ongoing disease activity. An in vivo study of atherectomy specimens from culprit lesions responsible for stable angina, unstable angina, or non-Q-wave myocardial infarction\textsuperscript{[33]} showed that culprit lesions responsible for the acute coronary syndromes contained significantly more macrophages than did lesions responsible for stable angina (14\% versus 3\% of plaque tissue occupied by macrophages).

Macrophages are capable of degrading extracellular matrix by phagocytosis or by secreting proteolytic enzymes, such as plasminogen activators and a family of matrix metalloproteinases (MMPs; collagenases, gelatinases and stromelysins), that may weaken the fibrous cap and thus predispose to rupture. Several studies have identified MMPs in human coronary plaques\textsuperscript{[34,35]}, and lipid-filled macrophages (foam cells) may be particularly active in destabilizing plaques\textsuperscript{[36]}. A wide variety of cells apart from macrophages (mast cells) may produce MMPs. They are secreted in an inactive form and are activated by plasmin in the tissue, after which MMPs are capable of degrading virtually any connective tissue component (Fig. 1).

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**Cap fatigue**

Repetitive cyclic stresses weaken structures and increase their proneness to fracture, leading to mechanical failure caused by fatigue. Cyclic stretching, compression, bending, flexion, shear and pressure fluctuations may fatigue and weaken a fibrous cap, which ultimately may rupture spontaneously (i.e. unprovoked or untriggered). Lowering the frequency (heart rate) and magnitude (flow- and pressure-related) of loading should reduce the risk of plaque disruption if fatigue plays a role\textsuperscript{[42]}.

**Triggers of plaque disruption**

Coronary plaques are constantly stressed by a variety of mechanical and haemodynamic forces that may precipitate or ‘trigger’ disruption of vulnerable plaques. Stresses imposed on plaques are usually concentrated at the weak points discussed above, namely at points at which the fibrous cap is thinnest and where tearing most frequently occurs\textsuperscript{[43]}.

According to Laplace’s law, the tension created in fibrous caps of mildly or moderately stenotic plaques is greater than that created in caps of severely stenotic plaques (smaller lumen) with the same cap thickness and exposed to the same blood pressure. Consequently, mildly or moderately stenotic plaques are generally stressed more than severely stenotic plaques, and could therefore be more prone to rupture.

Bleeding and/or oedema into plaques from the thin-walled new vessels originating from the vasa vasorum frequently found at the plaque base\textsuperscript{[44,45]} could theoretically...
increase the intra-plaque pressure, with resultant cap rupture from the inside\cite{40}. Collapse of severe but compliant stenoses due to negative transmural pressures may produce highly concentrated compressive stresses from buckling of the wall with bending deformation, preferentially involving plaque edges, and theoretically this could contribute to plaque disruption\cite{47}. The propagating pulse waves cause cyclic changes in lumen size and shape, with deformation of plaques, particularly the ‘soft’ ones\cite{48}. Eccentric plaques typically bend at their edges (at the junction between the stiff plaque and the more compliant plaque-free vessel wall). Also, changes in vascular tone cause bending of eccentric plaques at their edges. Cyclic bending may in the long term weaken these points, leading to unprovoked ‘spontaneous’ fatigue disruption, whereas sudden accentuated bending may trigger rupture of a weakened cap. Haemodynamic stresses are usually much smaller than mechanical stresses imposed by blood and pulse pressures\cite{49}. Theoretically, fluttering of severe but compliant stenoses between collapse and patency\cite{50,51} and turbulent pressure fluctuations distal to severe asymmetric stenoses could fatigue the plaque surface, promoting plaque disruption\cite{52}.

**Therapy**

How may we interrupt the dangerous and progressive sequence of events that ultimately lead to coronary thrombosis and to clinical events? The most obvious way to avoid occlusive or mural thrombosis is to try to block thrombogenesis. During the past few decades this was addressed with the use of various agents, including heparin, aspirin, ticlopidine and, most recently, glycoprotein IIb/IIIa receptor antagonists. Whatever the way in which inhibition of thrombogenesis is achieved, however, it is not possible to predict when plaque disruption may occur and hence administer antithrombotic treatment at the appropriate time point.

The term ‘passivation’ appeared for the first time in a report from the Mount Sinai Group\cite{53} and focused on inhibition of thrombogenesis by direct platelet inhibition with glycoprotein IIb/IIIa receptor antagonists. These drugs may also be of help as adjunctive therapy in patients undergoing percutaneous transluminal coronary angioplasty with or without stent implantation, thanks to their capacity in the short term to reduce abrupt vessel closure and coronary thrombosis, and in the long term to decrease significantly the composite incidence of death, acute myocardial infarction and urgent revascularization. In patients with unstable angina/non-Q-wave myocardial infarction, the adjunctive use of glycoprotein IIb/IIIa blockade may promote stabilization of the ruptured plaque and cause changes in the vessel wall, rendering it an inert surface that is incapable of supporting further platelet activation (so-called ‘passivation’) and thus preventing subsequent cardiovascular events\cite{54–57}.

Interventions that alter the vulnerability of plaques to disruption as well as propensity for thrombosis may reduce clinical events even without demonstrable changes in plaque volume or in the severity of stenosis. The more complicated but much more fruitful way to try to prevent plaque disruption is to interfere with the chain of events that eventually lead to plaque destabilization and rupture. There is much indirect evidence that plaque stabilization could be a crucial therapeutic intervention to combat the harmful consequences of coronary atherosclerosis.

The results of statin trials appear to indicate further actions that would reduce the tendency of plaques to break, thereby providing a reactive surface for platelets and clotting factor. In fact, not only can cholesterol lowering reduce metalloproteinase activity, but also statins have important effects on neointimal hyperplasia; they modulate leucocyte infiltration into the arterial wall, migration and proliferation of monocytes, and enhance cell apoptosis\cite{58}. Moreover, statins can reduce cholesterol synthesis by macrophages in the vessel wall; improve endothelium-derived relaxing factor formation; and reduce platelet aggregation, and concentrations of blood clotting factors\cite{59} and plasminogen activator inhibitor-1, thereby improving the thrombosis–fibrinolysis equilibrium. The important role played in plaque activation by oxidized low-density lipoprotein, which causes chemotaxis and activation of monocytes, cytotoxicity and hypercoagulability, draws attention to the protective effect of vitamin E and of foods that contain antioxidant agents, such as green tea, vegetables, fruit and olive oil.

**Conclusion**

Atherosclerosis without thrombosis is an asymptomatic disease. However, acute thrombosis frequently complicates the evolution of atherosclerosis, causing cardiovascular, cerebrovascular and peripheral events. The mechanism is usually plaque disruption with superimposed thrombosis, but not every plaque disruption is symptomatic. Major determinants of the vulnerability of a plaque to rupture are size and consistency of the atheromatous core, thickness of the fibrous cap covering the core, and ongoing inflammation within the cap. Plaque disruption tends to occur at points at which the plaque surface is weakest and most vulnerable, which coincide with points at which stresses resulting from biomechanical and haemodynamic forces that act on plaques are concentrated. Plaque passivation may be achieved in the short-term by agents that interfere with plaque-related thrombosis, and in the long-term by agents that counteract the mechanisms that underlie plaque activation and rupture.

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