PLAQUE INSTABILITY IN ACUTE CORONARY SYNDROME

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The spectrum of acute coronary syndrome (ACS) is broad and encompasses myocardial infarction as well as unstable angina. Coronary atherosclerosis is a chronic, slowly progressive disease, and has been shown to begin in its early stages even in the teenage years [1,2]. While in some patients coronary artery disease (CAD) is not symptomatic until a coronary lesion has progressed to cause a greater than 70% luminal stenosis, many patients present to medical attention with acute myocardial infarction before every having been diagnosed with CAD [3]. It is now understood that a majority of acute myocardial infarctions occur following rupture of an atheromatous plaque which had caused less then 50% vessel stenosis prior to rupture [4,5]. In contrast, for reasons that are not completely understood, atheromatous plaques which cause > 70-80% vessel stenosis are less likely to acutely rupture and result in ACS. Plaque rupture leads to myocardial ischemia and infarction by triggering platelet activation and activation of the coagulation cascade, resulting in thrombus formation which severely limits blood flow in the affected artery. In patients with ST-segment elevation myocardial infarction on electrocardiogram (STEMI), the resulting thrombus formation results in vessel occlusion, while in patients with non-ST elevation myocardial infarction (NSTEMI) or unstable angina, the resulting thrombus does not result in vessel occlusion in the majority of patients. The factors which predispose an atherosclerotic lesion to rupture are incompletely understood, but include plaque characteristics as well as vascular dysfunction, inflammation, and genetic predispositions.

Characteristics of plaque composition, such as the size and consistency of the atheromatous core and the thickness and composition of the fibrous cap may affect a lesion’s propensity to rupture. In contrast, the common finding of coronary calcification has not been associated with plaque instability or propensity for plaque rupture [6]. Studies using angioscopy and intravascular ultrasound (IVUS) have demonstrated that plaques with an increased lipid content and thin fibrous cap are associated with a higher incidence of acute ischemic events [7,8]. Plaques which are highly distensible are also more prone to rupture [9]. The Glagov effect (Figure 1) describes the phenomenon of positive arterial remodeling in which a vessel under increasing atheroma burden progressively dilates, effectively decreasing the degree of luminal stenosis [10]. Such remodeling has been associated with plaques with high lipid content, increased macrophage activity, and a propensity for rupture [11].

Vascular inflammation and plaque degradation have been linked to plaque instability in a variety of settings. Inflammation may be present not only in a vulnerable atheromatous plaque, but also more generally in the coronary and systemic circulations. Plaque histology has demonstrated that in the setting of endothelial dysfunction (associated with risk factors such as hyperlipidemia, hypertension, smoking, and diabetes mellitus) cytokine release leads to the recruitment of activated macrophages (foam cells) at the margins of atherosclerotic lesions. These inflammatory cells may infiltrate the vascular wall and may be stimulated to release metalloproteinases (MMP’s) which lead to matrix degradation and plaque instability [12,13]. Studies demonstrating a greater incidence of cardiovascular events in patients with high circulating levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) suggest that a more systemic increase in inflammatory activity predispose to plaque
instability as well. In fact, CRP has been demonstrated to independently predict cardiovascular events even after correction for more traditional cardiac risk factors [14,15]. CRP acts on vascular endothelial cells to induce cytokine secretion and thus promotes leukocyte adhesion. Furthermore, CRP acts directly at the endothelial cell level to diminish nitric oxide production and induce endothelial cell apoptosis. These data suggest that in vulnerable patients with increased markers of systemic inflammation, the factors leading to plaque instability may occur simultaneously at numerous different sites of coronary atherosclerosis. This notion is supported by a study demonstrating increased myeloperoxidase activity in both the coronary and systemic circulations in patients with unstable angina, and increased myeloperoxidase activity in both the left and right coronary circulations in such patients irrespective of the location of the culprit lesion [16].

Genetic factors predisposing patients to coronary artery disease and myocardial infarction are the topic of extensive research at this time. The thrombospondin gene was the first gene to be linked to premature CAD and myocardial infarction. Thrombospondin 1 and 2 are known to be potent suppressors of angiogenesis. A missense variant of thrombospondin 1 has been associated with an 11-fold higher rate of cardiovascular events, while a variant of thrombospondin 2 is protective [17]. 5-lipoxygenase activation peptide (FLAP) plays an important role in arterial inflammation, and a variant of the FLAP gene has been associated with a 2-fold increased risk of myocardial infarction [18,19]. The Apo E-4 allele is associated with elevated levels of low-density lipoprotein (LDL) cholesterol and a higher incidence of coronary artery disease [20]. The incidence of the Apo E-4 allele was demonstrated to be higher in a population of patients with prior myocardial infarction [21]; however, a direct link between the gene phenotype and myocardial infarction has not been established. Lymphotixin-α (LTA) is a proinflammatory cytokine expressed by macrophages and smooth muscle cells, with a broad range of immunological activities. The CC allele is associated with a higher incidence of CAD, while the TT allele is protective. A link between LTA and myocardial infarction has not been established [22].

The benefits of several therapies currently proven to reduce coronary events may be at least partially due to effects on plaque stabilization. Aspirin therapy may reduce the levels of circulating inflammatory cytokines which have been associated with plaque vulnerability. Statin therapy has been linked to plaque stabilization through anti-inflammatory effects in addition to decreased platelet aggregation and improvements in endovascular function. Beta-blockers, ACE-inhibitors, and angiotensin receptor blockers (ARB’s) may lower shear stress across vulnerable plaques through their effects on heart rate and blood pressure, thereby lessening the likelihood of rupture. Further research may involve more therapy with more specific inhibitors of the inflammatory processes or genetic predispositions underlying plaque instability and rupture. One example involved a study of FLAP inhibition in patients with myocardial infarction and the at-risk variant of the FLAP gene, which demonstrated a 25% reduction in CRP and a 26% reduction in leukotriene B4 with therapy [23].

Summary

Cardiovascular disease remains the leading cause of morbidity and mortality in the developed world. Atherosclerotic disease begins in its early stages at a young age and progresses chronically over many years. The multiple factors which lead to atherosclerotic plaque vulnerability leading to acute coronary syndrome are incompletely understood. Recent advances
have furthered our understanding of plaque composition, vascular inflammation, and endothelial dysfunction as well as predisposing genetic factors which contribute to plaque instability, and are leading to more targeted therapy. Further identification of the multifactorial processes leading to plaque vulnerability may allow for targeted therapy to stabilize such plaques before they rupture and significantly reduce the incidence of acute coronary syndrome and their resultant morbidity and mortality.

References


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Figure 1. Progression of Coronary Atherosclerosis and the Process of Plaque Disruption. Cross sections of the coronary artery are shown during successive stages of atheroma progression. See text for additional details. Adapted with permission from Lippy P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365-72.