Plaque Vulnerability, Plaque Rupture, and Acute Coronary Syndromes (Multi)-Focal Manifestation of a Systemic Disease Process

Paul Schoenhagen, MD; E. Murat Tuzcu, MD; Stephen G. Ellis, MD

In this issue of Circulation, Rioufol et al1 describe the presence of multiple ruptured atherosclerotic coronary plaques in patients presenting with an acute coronary syndrome (ACS). With the use of intravascular ultrasound (IVUS), the authors systematically examined proximal portions of the entire coronary tree in 24 patients. Ruptured plaques were found at the culprit lesion in 9 patients (37.5%) but, more importantly, distant from the culprit lesion in 19 patients (79%). These additional ruptured plaques were frequently multiple, located in a vessel different from the culprit vessel in 70% of patients and in 2 vessels not related to the acute event in 12% of patients. Both culprit lesions and additional ruptured plaques were characterized by positive remodeling. The authors proceeded with coronary stent placement at the culprit lesion site in 19 patients (86%) and, on the basis of angiographic and IVUS criteria (minimum luminal diameter <1.5 mm, minimum luminal cross-sectional-area <4 mm²), at additional sites in 16 patients (72%).

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It is important to consider these findings in the context of the recent literature. Traditional diagnostic criteria of lesion significance define focal, hemodynamically significant plaques that cause acute or chronic impairment of coronary blood flow. These lesions are identified by selective coronary angiography. However, it is well known from angiographic studies that most myocardial infarctions occur at sites that previously caused only mild-to-moderate luminal stenosis.3 In histological studies of patients with coronary artery disease who died suddenly, the plaque at the culprit lesion site shows evidence of rupture in ~70% of patients and superficial erosion in 30% of patients.3 Acute superimposed thrombosis leads to luminal obstruction.

Similar to the findings of Rioufol et al,1 other recent studies that used different clinical imaging modalities found evidence of ruptured plaques that were distant from the culprit lesion in patients with acute cardiovascular events. Goldstein et al4 reported the presence of additional complex angiographic lesions in ~30% of patients presenting with ACS. Many of these lesions were found in vessels not related to the acute event. While these studies examined plaques that had already ruptured, coronary angioscopy can identify lesion characteristics presumably associated with a propensity to undergo rupture. In an angioscopic study, Asakura et al5 reported the frequent presence of “vulnerable, yellow” coronary plaques distant from the culprit lesion in patients with ACS. Similarly, thermal heterogeneity within human atherosclerotic coronary arteries has been documented with the use of special thermography catheters.6 Areas with higher temperatures are thought to be associated with plaque instability. In subsequent studies, temperature heterogeneity has been found to be larger in patients presenting with ACS.7

These clinical findings support our present understanding of the pathophysiology of coronary artery disease.8 Rather than a simple mechanical problem, the development of coronary lesions is a complex biological process. The transition to an unstable atheroma is characterized by the accumulation of a large necrotic core, containing extracellular lipids, macrophages, and often microcalcifications. These unstable, vulnerable sites are frequently not highly stenotic before rupture because the accumulating plaque is accommodated by positive remodeling, alleviating the reduction of luminal size.9,10 Both positive remodeling11 and eventual plaque rupture2 are related to an inflammatory response, supporting the role of systemic inflammation in patients with a high propensity for acute coronary events.12

Lesion stability appears to be a continuum with biologically inactive, but sometimes hemodynamically significant lesions on the one hand, and biologically active, vulnerable lesions that lead to ACS on the other. Importantly, although pathological studies have demonstrated that the sequence of plaque rupture and subsequent thrombus formation is the initiating event of most ACS,2,3 rupture of a coronary atheroma appears to be a frequent event that only occasionally leads to luminal obstruction. Therefore, many vulnerable plaques that rupture do not cause a clinical event. Presumably, patients presenting with ACS have an underlying (temporary?) biochemical milieu predisposing them to the development of widespread plaque degeneration and/or accelerated subsequent thrombus formation. The occluding thrombus at the culprit lesions determines the clinical presentation but is only the focal manifestation of an underlying systemic disease process. It is not clear why some plaques lead to clinical manifestations, whereas many others remain asymptomatic and heal with subsequent fibrosis, frequently associated with luminal narrowing.13

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Correspondence to Stephen G. Ellis, MD, Sones Cardiac Catheterization Laboratories, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, F-24, Cleveland, Ohio, 44195.

E-mail: elliss@ccf.org

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These findings are consistent with clinical observations. Sudden rupture of a previously hemodynamically insignificant lesion would explain why acute myocardial infarction and sudden cardiac death frequently occur in patients without prior symptoms of coronary artery disease.3,13 The high incidence of recurrent events in patients with acute myocardial infarction, which correlates with systemic markers of inflammation,14 may be related in part to additional vulnerable lesions distant from the culprit lesion.

What are the clinical implications of these findings for the diagnostic and therapeutic approach to patients with ACS and those at risk for such events? The diagnosis of vulnerable lesions before rupture would have tremendous potential for event prevention. Several approaches are presently being explored: IVUS, along with other invasive and noninvasive imaging modalities, could allow the assessment of individual plaques and overall plaque burden.15,16 The tagging of markers specific to activated, vulnerable plaques could further enhance imaging techniques. Other diagnostic approaches could assess the biochemical activity by either measuring the local temperature heterogeneity6,7 or biochemical markers, as exemplified by C-reactive protein.12 These present approaches have tremendously advanced our understanding of plaque vulnerability and rupture, but several questions remain unsolved:

- Will it be more important to identify individual vulnerable lesions or the number of vulnerable lesions at any one time?
- Is a plaque that has recently ruptured as dangerous as a plaque before rupture?
- When does a ruptured plaque lose its potential to form a superimposed thrombus?

An optimal diagnostic test would be noninvasive, safe, and easily repeatable. It would not only identify vulnerable and ruptured lesions but also differentiate plaques that are more likely to cause ACS. Such a test does not yet exist.

The treatment of hemodynamically insignificant lesions with characteristics of vulnerability or rupture is equally or more challenging. The diffuse distribution of these lesions may suggest that a systemic treatment would be most beneficial. It has been postulated that the success of common systemic treatments of patients with ACS (eg, platelet-receptor inhibitors and lipid-lowering medications)17,18 may imply that this site is still biologically active. The surprisingly low number of evident ruptures at the culprit lesion site is also noteworthy. As the authors point out, this could be caused by limitations of IVUS to differentiate between thrombus and atheroma. A superimposed thrombus at the culprit lesion site may mask the underlying rupture. This has important clinical consequences for patients presenting with ACS: In the presence of a ruptured plaque with superimposed acute thrombosis and additional lesions, the accurate identification of the culprit lesion may not always be possible.

The findings of Rioufol et al support the growing body of evidence that coronary artery disease is a systemic disease of the entire coronary tree. Further research is needed to illuminate the complex relation between focal manifestation and overall disease burden. In the meantime, the present approach to patients with ACS, which includes the focal treatment of the hemodynamically significant culprit lesion (including antiplatelet therapy)17 as well as systemic treatment (eg, statins, β-blockers, and ACE inhibitors),19 remains the clinical standard and may already affect lesions distant from the culprit site.

References


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