Vulnerable Plaque
The Devil Is in the Details
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The notion of “vulnerable atherosclerotic plaque” introduced many years ago has been since used frequently and liberally, including by this investigator. We generally use this phrase to refer to intact lesions that look similar to those previously found to be disrupted and complicated by thrombosis on pathological examination. In doing so, we assume that given enough time or the right stimulus, these would become disrupted, thus triggering the formation of a thrombus. In an attempt to transform the potentiality into certainty, Virmani and colleagues have proposed that a descriptive terminology based on pathological characteristics of atherosclerotic lesions should be used instead. They proposed that the precursor lesion for disrupted plaques should be referred as “thin-cap fibroatheroma” (TCFA), a terminology that should encompass, along with ruptured plaques, the other types of plaques triggering thrombosis, ie, eroded plaques and calcified nodules. TCFA of patients dying from acute myocardial infarction are usually associated with <50% diameter stenosis, explaining the relatively recent realization of the danger these plaques may harbor. Other overall characteristics commonly associated with ruptured plaques include their propensity to have an eccentrically located lumen, as well as the significantly enhanced compensatory enlargement of the affected segment.

Getting Up Close and Personal
Morphologically, ruptured plaques are characterized by a thin fibrous cap covering a necrotic core containing macrophages and interstitial collagen, calling for improved imaging techniques that can reveal this level of structural detail in the plaques of patients. The precise measurements that can be performed on pathological specimens have yielded detailed dimensional parameters. For instance, the area of the necrotic core in at least 75% of cases of ruptured plaques examined was reported to be ≤3 mm². Unfortunately, such precision is beyond the current capability of most currently used imaging techniques, limiting the possibility of identifying TCFA in clinical settings. However, other than the current efforts to improve the resolution of current imaging techniques, novel imagining modalities are being developed based on the specific identification of reported hallmarks of inflammation and necrosis of TCFA, such as protease activity, endothelial cell adhesion molecules, or apoptotic macrophages.

Do Some of Us Become Easy Targets?
In addition to sharing morphological characteristics of the plaque itself, the occurrence of disruption seems to become a more likely clinical event in patients who share some common systemic signs, including high serum total cholesterol, a high total cholesterol to high-density lipoprotein cholesterol ratio, and elevated levels of C-reactive protein (CRP). Such associations have prompted the notion of a “vulnerable patient” who is likely to have more than one vulnerable lesion. For many of these systemic characteristics, it still remains unclear if they are the cause or the effect of lesion vulnerability. A similar question continues to apply to any of the newly proposed systemic or local factors that have been associated with plaque instability, including the matrix metalloproteinases (MMPs).

Guilty by Association?
MMPs, a family of related proteolytic enzymes with over 20 known members, have become prime suspects for creating plaque vulnerability because of their best-known biological activity of degrading extracellular matrix components, likely to lead to loss of mechanical properties of tissues displaying active MMPs. Increased expression of several MMPs and of proteolytic activity attributable to MMPs was reported to be associated with vulnerable shoulders of atherosclerotic plaque 10 years ago, and numerous pieces of evidence have been gathered in support of MMP family association with the pathological remodeling of blood vessels. The concept of MMP involvement in the natural history of the atherosclerotic plaque has proved to be extremely fruitful in terms of offering a working mechanistic support for the notion of vascular remodeling, which has changed the way we understand, investigate, and diagnose atherosclerotic disease. On the other hand, despite the growing literature associating MMPs, definitive evidence of the causative role of MMPs in plaque destabilization is still missing. Similarly, there is a continuing paucity of data regarding the mechanical properties of various plaques, specifically of their relation with vulnerability, prompting calls to the development of an assessment scale for plaque vulnerability.

Are There Several MMPs Ganging Up to Disrupt the Plaque?
Previous studies have suggested that MMP-9 and the study in this issue by Molloy et al suggests that MMP-8 are
specifically associated with plaque vulnerability. The study by Molloy and colleagues[16] is expanding on the previously reported association between MMP-8 and atherosclerotic lesions.[17] In this earlier study based on the comparative histological investigation of a smaller number of specimens, Herman et al[17] reported that MMP-8 expression was increased in atherosclerotic lesions versus normal arterial tissue. They also associated MMP-8 expression mostly with the presence of macrophages. In the current study by Molloy et al,[16] the authors included clinical investigation of patients and thus were able to divide the atherosclerotic plaques on the basis of clinical and histological presentations. The authors report significantly higher levels of active MMP-8 in the plaques of patients with preoperative clinical symptoms, as well as in patients who developed emboli, and in the plaques showing histological evidence of disruption. Therefore, the correlation between increased activity of MMP-8 with accepted signs of vulnerability is likely clinically relevant, but as in the other cases, it remains unclear whether MMP-8 is the culprit or rather the marker for plaque instability. Increased MMP-8 expression in the lesion could be potentially explained by the increased percentage of macrophages, a characteristic feature of disrupted plaques, or MMP-8 could be perhaps a systemic non-specific marker of disease states associated with inflammation[19] or otherwise significant remodeling of tissues.[19] One of the potential limitations of the current study[16] is the a priori selection of the MMPs to be investigated (MMP-1, MMP-8, and MMP-13) based on the postulation that only those MMPs that can degrade fibrillar collagen would be relevant for plaque instability. This choice may be unfortunate because recent biochemical evidence suggests that other MMPs detected in the vulnerable plaques may actually work as collagenases.[20] In addition, even if from a pure assessment of mechanical properties interstitial collagen content is the major determinant of mechanical strength of tissues, other substrates for various MMPs, which include matrix components or local biologically active factors, are likely to affect collagen metabolism[21] or its supramolecular assembly, and potentially other aspects of plaque stability. The authors’ choice[16] has specifically eliminated an opportunity to provide support for or challenge to the previously reported association of increased local[14] and systemic[15] levels of MMP-9 and plaque instability.

Should We Shoot the Messenger? The demonstration of MMPs as a cause for plaque vulnerability, as previously suggested, is still awaiting the availability of proper experimental models to test the connection between MMPs and plaque rupture, as well as the development of selective MMP inhibitors.[12] A reassuring thought is that if MMPs, specifically MMP-8, are indeed the cause of plaque vulnerability, therapeutic inhibition seems to be already possible. Long-term doxycycline treatment of patients with reactive arthritis decreased serum MMP-8 levels.[18] An unsettling thought is that increased levels of MMP-8 may represent the intent to heal, as suggested by studies showing that MMP-8 is the predominant collagenase in healing wounds[22] and non-healing ulcers.[23] In a similar twist of events, recent results prompted the proposal that MMP-9 is important in wound healing.[24] This new concept was based on the unexpected findings that MMP-9, known and pursued for its matrix degrading capacity, is actually contributing to the reorganization of collagen monomers into fibrils and to contraction of collagen gels, both essential for wound healing and for increasing the mechanical strength of tissue. Thus, MMPs are continuing to amaze us with their versatility, likely requiring careful reconsideration of plans to bluntly interfere with their actions. Meanwhile, we may be better served by considering MMPs as a sign of plaque vulnerability/instability until proven guilty.

As with all things truly evil, the very essence of plaque vulnerability—the modern plague that claims the lives of millions—continues to elude us. However, on the basis of many reported sightings, the composite sketch of the serial killer is slowly coming into focus.

Acknowledgments Funding for some of the studies conducted in the laboratory of the author was provided through the National Institutes of Health grant RO1 HL64689, the American Heart Association Established Investigator Award # 0040087N, and the National Science Foundation (NSF) Award EEC-9731643.


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Circulation. 2004;110:244-246
doi: 10.1161/01.CIR.0000135195.60131.59
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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