EDITORIAL COMMENT

The Vulnerable Plaque “Hypothesis”
Promise, but Little Progress*

Steven E. Nissen, MD
Cleveland, Ohio

A PubMed search using the terms “vulnerable plaque” or “high-risk” plaque yields >2,000 references to journal articles published over the past 20 years. Indeed, few concepts in cardiovascular medicine have achieved such intense scientific interest over such a long duration. During this 20-year period, many diagnostic techniques designed to “detect” vulnerable plaques have come and gone. In each case, a flurry of promising “findings” has been followed by a sobering reality check. These include thermography, spectroscopy, palpography, virtual histology, optical coherence tomography, and many more (1–5). A large number of startup companies with “breakthrough” approaches have come and gone, nearly all leaving investors with empty pockets, but no progress. What has gone wrong?

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It is time to face reality. Much of the contemporary concept of vulnerable plaque is fundamentally flawed or overly simplistic, and most approaches to detection are poorly conceived. Many of the proponents of vulnerable plaque detection have approached the problem with a naïve premise, namely, that one merely needs to detect the “high-risk plaque” and place a stent to preempt the “inevitable” plaque rupture that might threaten the life of the patient. The most ardent advocates have named this approach “plaque sealing,” and some have actually performed such interventions before large and rapt audiences at major interventional “demonstration” courses. However, this simplistic thinking immediately fails any reasonable scientific scrutiny. More thoughtful studies have revealed a biological reality that undermines the plausibility of the “let’s stent the vulnerable plaque” approach.

First, to “seal” vulnerable plaques, you must find them. However, most methods reported to date, including the approach used by Gonzalo et al. (6) in this issue of JACC, seek to identify a “surrogate” for the vulnerable plaque, specifically a lesion described as a “thin cap fibroatheroma” (TCFA). Based upon limited autopsy studies published by Virmani et al. (7), nearly all authors in this field of research assume that there is a direct 1-to-1 relationship between a TCFA and a high-risk plaque. However, in reality, there are few scientifically credible data supporting such a relationship. Accordingly, it is assumed, but not proven, that the presence of large numbers of TFCAs represents a harbinger of future vascular events.

After 20 years of research and countless clinical studies, has any method of detection of high-risk plaques successfully predicted which lesions are most likely to rupture, resulting in an acute event? Astonishingly, the answer is clearly “no.” There exist no prospective clinical trials demonstrating that presence of any specific plaque morphological feature is associated with a worse prognosis for patients. While it is true that autopsy studies suggest that TCFAs are most often the culprit lesions in acute coronary syndromes (ACS), it is quite another matter to show that the presence of this morphology prospectively predicts plaque behavior. In the absence of a proven relationship between TCFAs and adverse outcomes, improved

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methods for detection of such lesions constitute only an academic exercise.

Let us, for the moment, accept the premise that the TCFA is truly the vulnerable lesion. How might we utilize this knowledge to improve patient care and outcomes? First, we would need to find and “map” all of the TCFAs. Because acute cardiovascular events can involve any coronary vessel, we would need to examine all of the major epicardial arteries and their principal branches. These include not just the 3 major coronaries, but also large obtuse marginal branches, diagonal branches, and the posterior descending artery. In the case of the method proposed by Gonzalo et al. (6), 2 separate imaging modalities were employed. Such an approach would require subselectively placing a guidewire in no less than 5 or 6 major vessels and carefully interrogating the length of these vessels, not once, but twice. All of this must be accomplished without untoward events resulting from placement of mechanical devices in these modestly sized vessels.

Now let us, for the moment, assume that such a complete interrogation of the coronary circulation is feasible. What are we likely to find? Many thoughtful investigators have shown that plaque instability is a distinctly multifocal phenomenon (8). We are not likely to find “the” vulnerable plaque, because, in fact, a multitude of such high-risk lesions are likely present. Available data suggest that there may be dozens of lesions present, distributed throughout the coronary circulation. So, if we could find the vulnerable plaques, do we really think we could stent them all? If a handful of particularly high-risk lesions were detected and “sealed,” will the immediate risks and late adverse consequence of coronary intervention (late stent thrombosis) actually exceed any prospective benefits? The COURAGE (Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation) trial suggests that the risks of such a strategy may exceed any benefits (9).

There is also the issue of the temporal relationship between imaging procedures and vulnerability. Any diagnostic method for vulnerable plaque detection represents a snapshot in time. However, we have little information about the stability of plaque morphologic measurements over time. If a plaque is high risk today, will it be high risk in 1 month, 3 months, or a year from now? Intravascular ultrasound studies of the regression and progression of atherosclerosis suggest that the atheroma can change quite rapidly with medical therapy. If we stent a vulnerable plaque, are we potentially intervening with a lesion that is destined to become quiescent in a few weeks or months? Conversely, if we classify a location as stable, can we be certain that this site will not undergo acute conversion to a vulnerable lesion a few weeks from now?

We must understand that atherosclerosis is a systemic disease, strongly associated with inflammation and other widespread phenomena. In the months after an ACS, event rates remain elevated because the systemic factors leading to the ACS are still present. Stenting a few TCFAs will not change the systemic inflammatory milieu. However, attacking the underlying disease is feasible and has proven effective in many prospective trials. Statins, antiplatelet agents, smoking cessation, and other medical interventions lessen the likelihood of recurrence after an ACS. In contradistinction to the absence of progress in vulnerable plaque detection, medical therapies have dramatically lowered event rates after acute events during the past 20 years. These therapies work because they do not approach the “vulnerable plaque” phenomenon as a local problem; they attack the underlying systemic disease.

With this background in mind, the study by Gonzalo et al. (6) can be placed in perspective. It offers some scientific insight into the distribution of TCFAs near coronary bifurcations, but does not represent a practical approach to identification of vulnerable plaques. The approach also has important weaknesses. The definitions for various tissue types must be viewed as arbitrary, attempting to define a continuous phenomenon as a series of discrete variables. For example, a plaque with 9% necrotic core and cap thickness of 66 μm would not be classified as a TCFA, but a plaque with 11% necrotic core and 64 μm cap thickness would be a high-risk lesion. Such arbitrary rules make little biologic sense. In all likelihood, vulnerability is a continuous variable, not a binary “yes” or “no” phenomenon. The 2 lesions may have little difference in their actual risk of plaque rupture.

Research, such as the current study by Gonzalez et al. (6), should be encouraged, but we must accept that there is little likelihood of a near-term breakthrough yielding important patient benefits. For now, such studies must be considered exploratory.

Reprint requests and correspondence: Dr. Steven E. Nissen, Cleveland Clinic Foundation, Cardiovascular Medicine, 9500 Euclid Avenue, Desk F-15, Cleveland, Ohio 44195-0001. E-mail: nissens@ccf.org.
REFERENCES


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