Requiem for the 'vulnerable plaque'

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The concept of the so-called "vulnerable plaque" has proven highly useful to guide research and thinking regarding the pathophysiology of the acute coronary syndromes (ACS). Yet, the time may have come to reconsider this construct, as knowledge has accumulated, the risk profile of the populace has shifted, and our current therapies have reshaped the disease. Over the last several decades, the quest to identify and treat the "vulnerable plaque" has generated much interest.[1] Loaded with lipid, macrophage rich, covered by a thin fibrous cap, and considered perilously poised to rupture, the thin-capped fibroatheroma ("TCFA") has become a target for imaging, possible intervention, model attempts in animals, and much discussion.[2] Many equate type 1 myocardial infarction with "plaque rupture". Yet, the "vulnerable plaque" concept, as useful as it has proven heuristically, may not represent the contemporary challenge, an unmet clinical need, or a fertile field for future research.

Challenges to the "Vulnerable Plaque" Concept (Table)

The notion of the "vulnerable plaque" arose from autopsy studies that disclosed some 2/3 to 3/4 of fatal acute myocardial infarctions resulted from a fracture of the plaque's fibrous cap that engendered thrombosis (Figure 1.) The elegant post-mortem studies of pathologist pioneers redirected the cardiology community from confusion about the causality of thrombosis in ACS and a focus on vasospasm toward plaque rupture.[3, 4] However compelling, the number of ruptured plaques resulting in luminal occlusion in these autopsy studies lacked a "denominator". While such studies could interrogate the culprit of a fatal myocardial infarction, they did not

determine how many plaques with morphologic characteristics associated with vulnerability did *not* cause a fatal rupture.

More recent lines of evidence suggest that plaques with thin fibrous caps and large lipid pools actually seldom rupture and cause clinical events. Multiple "active" plaques often reside in the coronary and other arteries.[5-7] Intravascular imaging studies in humans using ultrasound or optical coherence tomography have proven particularly illuminating. Thin-capped plaques do not inevitably rupture and cause thrombotic events. Contemporary data do not support the "vulnerability" of TCFA, and indeed plaques of other morphologies may also give rise to thrombotic events as discussed below. "Virtual histology", a technique based on the analysis of information gleaned from intravascular ultrasound, while incompletely validated, has provided an important challenge to the "vulnerable plaque" concept. In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study only about 5% of thin-capped plaques as defined by virtual histology caused coronary events during a 3.4 year follow-up period.[8] As longitudinal intravascular imaging studies such as PROSPECT enrolled higher-risk patients, thin-capped plaques in lower risk populations may cause even fewer thrombotic events. Thus, the vast majority of so-called "vulnerable plaques" does not exhibit clinical "instability" and indeed seldom provoke acute coronary syndromes. Moreover, the consequences of a plaque disruption depend not only on the "solid state" of the atheroma itself, but also on the "fluid phase of blood, for example the concentrations of fibrinogen, endogenous inhibitors of fibrinolysis, and pro-coagulant microparticles.[9]

Have Statins and Other Preventive Measures Altered the Mechanisms of ACS?

Over the years the etiology and pathophysiology of many cardiovascular diseases have evolved. Consider the receding importance of rheumatic heart disease that once dominated valvular heart disease, now surpassed by other valvulopathies. Endocarditis also underwent a "sea change" due to shifting demographics, socioeconomic factors, and the advent of antibiotics. Lerner and Weinstein, in a landmark series of articles in the *New England Journal of Medicine* in 1966, bore witness to the shifts in bacterial endocarditis in the "antibiotic era".[10] The patient population at risk also evolves. Although percutaneous interventional strategies have yielded a decline in the acute mortality due to ST segment elevation myocardial infarction (STEMI), the survivors may develop more heart failure in the long-term.

We contend that we currently find ourselves amidst a shift in disease manifestations of atherosclerosis due to altered demographics, attendant changes in risk factor profiles, efforts to control tobacco abuse, and the increased prevalence of statin treatment. Myocardial infarction has "gone global", not only affecting predominantly middle age Caucasian males in higher socioeconomic strata, and no longer associates mainly with cigarette smoking, hypertension, and high LDL. Women, non-Caucasians, younger individuals, and those with obesity, insulin resistance or frank diabetes, and high triglycerides and low HDL represent an increasing proportion of our patients with ACS.

We also now find ourselves the midst of a transition in the presentation of ACS, with STEMI on the wane and non-ST segment elevation myocardial infarction (NSTEMI) rising.[11]

While much of the increase in NSTEMI might result from the introduction of ever more sensitive troponin assays, shifting acute coronary syndromes previously classified as "unstable angina" to NSTEMI, the decline in STEMI and rise in NSTEMI began before the use of such assays. The temporal decline in STEMI incidence accompanies a substantial decline in stroke incidence and case fatality.[12, 13] These findings strengthen our proposition regarding a transition in the pathological mechanisms and presentations of the acute complications of atherosclerotic disease.

Concomitant with this trend from STEMI dominance toward NSTEMI, statin use has risen.[14] While the temporal coincidence of a shift in ACS pathogenesis and the penetration of statin therapy does not prove causality, substantial evidence supports such a relationship. Animal studies show that lipid lowering and/or statin treatment can reinforce the fibrous cap, decrease the lipid pool, and reduce inflammation.[15] Human imaging studies buttress the notion that statin therapy reduces the lipid content of plaques and augments the proportion of the plaque comprised of fibrous tissue, a characteristic associated with resistance to rupture.[16, 17] Studies on retrieved atherosclerotic plaque specimens in the Athero-Express collection have shown a time-dependent shift in the morphology of human atherosclerotic plaques over the last dozen years or so. Plaques obtained from more recent patients with symptomatic carotid artery disease reveal significantly more fibrous, non-inflammatory characteristics. This temporal trend toward plaques with morphologic characteristics of "stability" in biobanked plaques also applied to asymptomatic patients. Surprisingly, statin use only explains part of this shift towards more fibrous lesions. Thus, other determinants merit careful consideration, including public policies that reduce passive smoking. Analysis of the histologic features of more than 1500 plaques

showed that large atheromata with high macrophage content have significantly declined from 2002 – 2011, supporting our contention that the classical notion of the "vulnerable plaque" has receded in relevance.[18] Although obtaining plaque suitable for analysis from human coronary arteries presents challenges, the change in characteristics observed in human carotid atheromata likely sheds light on the current STEMI/NSTEMI transition.

Is the Dominant Mechanism of Coronary Thrombosis Shifting from Plaque Rupture to Superficial Erosion?

The oft-quoted autopsy studies that classified culprit lesions of ACS morphologically found that rupture of the fibrous cap more commonly accounted fatal acute myocardial infarction than superficial erosion. Work from several leading pathologists has identified superficial erosion as a cause of ACS, and highlighted the characteristics of lesions associated with fatal erosion that actually contrast quite starkly with those attributed to ruptured plaques (Figure 1).[2] As opposed to lesions associated with plaque rupture, those that underlie superficial erosion do not have thin fibrous caps. They harbor fewer inflammatory cells. They lack large lipid pools. Rather than insufficient interstitial collagen, lesions that cause superficial erosion accumulate abundant extracellular matrix, notably proteoglycan and glycosaminoglycans.[19] Superficial erosion occurs more commonly in women, in individuals with diabetes, and the elderly. This clinical profile reflects in many ways the changing demographics of individuals who present with ACS today. As noted above, lipid lowering, in particular statin treatment, and perhaps less

passive smoking, may modify the characteristics of the atherosclerotic plaque in a way that thickens the fibrous cap, reduces lipid accumulation, dispels inflammation, and shrinks the volume of the lipid core. These morphologic changes should lead to "stabilization" of plaques, reducing their risk of rupture. Do statins and other current treatments reduce plaque rupture as a cause of ACS? Such a pharmacologically induced transition in the proportion of ACS and strokes caused by erosion versus rupture could echo the changes in the clinical syndromes of endocarditis ushered in by antibiotic availability.

Might a shift toward superficial erosion versus rupture as a mechanism of thrombosis contribute to the decline in STEMI and concurrent rise in NSTEMI, or to decreased death following some strokes? While this conjecture remains speculative, emerging evidence provides hints that favor this hypothesis. Contemporary optical coherence tomography studies have shown not only a growing proportion of ACS due to erosion versus fibrous cap rupture, but also provide preliminary evidence that erosion associates more frequently with NSTEMI than STEMI (Figure 2).[20, 21]

Clinical Implications and the Importance of the Evolving Mechanisms of ACS

One often hears that military leaders face today's battle equipped to fight yesterday's war. While plaque rupture has dominated our thinking about type 1 myocardial infarction for decades, current data should spur us to consider the shifting demographics, epidemiology, and pathophysiology of the ACS to confront this growing worldwide scourge most effectively. We

have made considerable inroads into understanding the pathophysiology of the "vulnerable plaque", and our current therapies have begun to contain this epidemic, although we must strive to maximize the appropriate application of these proven preventive measures.[15] The changes in clinical manifestations and the concomitant shift in plaque characteristics underlying thrombotic disease have many implications for research as well as the clinic. Many investigators have attempted to mimic in animals plaques that resemble thin-cap fibroatheromata. Much effort has gone to developing imaging technologies that identify single so-called "vulnerable" lesions, a potential fool's errand in light of current data.

Despite the measures that modify so-called "vulnerable plaques", a considerable burden of residual risk remains even in the statin era. The statins may have contributed to this evolution, and the introduction of new therapies that reduce LDL even further may provide yet more benefit. The shift in the risk factor profile in our ACS patients today highlights the need for novel therapies. Those that address HDL, triglyceride-rich lipoproteins, and inflammation exemplify targets beyond LDL that may address the risk factor profile of those susceptible to residual events in the statin era.

While we can take some satisfaction with our progress to date in understanding and taming the "vulnerable plaque", we should not relax our guard, and must martial all of our resources to address the residual balance of risk in our patients both mechanistically and therapeutically. We should pursue the pathophysiology of plaque erosion in greater depth so that we can prepare to address its fundamental causes, as we have done for decades in the case of plaque rupture.

Table 1:

Challenges to the "Vulnerable Plaque" Concept

• Thin-capped, lipid-rich atheromata are not solitary, rather often multiple, and affect several arterial beds in the same individual

• Thin-capped, lipid-rich atheromata most often persist for years without causing a clinical event

• The risk profile and demographics of ACS patients is shifting worldwide (global burden, younger patients, more women, more insulin resistance/diabetes, more hypertriglyceridemia, less LDL excess)

• Statin treatment and other preventive measures have begun to modify atherosclerotic disease

• STEMI wanes as NSTEMI waxes

• Plaque rupture declines as a cause of ACS while superficial erosion appears on the rise

• Plaques underlying cerebrovascular events reveal more stable fibrous characteristics compared with 10 years ago.

Figure legends:

Figure 1: Contrasts between superficial erosion and fibrous cap rupture as causes of arterial thrombosis.

Figure 2: NSTEMI associates more frequently with superficial erosion than with plaque rupture. Data are derived from ref. 19.

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