Another Calcium Paradox?

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In a number of important diseases, the clinical course is defined principally by the host response, more so than by the initiating environmental insult. Clinicians rely on identification of this host response for diagnosis and may select those responses as targets for therapeutic intervention. Atherosclerosis is one such disease. The clinical course was once felt to result from progressive accumulation of inert “deposits” of cholesterol and calcium. In the past decade, it has become clear and widely understood that atherosclerosis is a complex orchestrated series of host responses to as yet poorly understood vascular injury. One of the most striking and convincing mechanistic advances in recent times has been the revelation of the extent to which inflammatory events predominate in the afflicted arterial wall. This understanding has been reached by basic and clinical studies at the tissue, cellular, and subcellular levels and by population-based epidemiological investigations. The atherosclerotic process can be viewed as occurring in stages, beginning with a “nascent” period, during which fatty streaks appear in the arterial wall. Transformation to a “hot” phase ensues, consisting of accumulation of free lipid, leukocyte attraction and activation, and proliferation of arterial wall cells. This phase, the paradigm holds, gives way to lipid resorption, collagen deposition and remodeling, and calcification of vessel wall tissue. We now know that mural calcification, once thought to represent a “burned out” stage of atherosclerosis, is actually a complex programmed process that bears morphological and biochemical resemblance to bone formation. This conceptualization of atherosclerosis is complicated by recognition that >1 phase of the process is frequently present in the arteries of a given patient or experimental animal and, in fact, can be present within the same plaque.

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Because the ravages of atherosclerosis accrue from this series of host responses, it is appropriate for clinicians and researchers to search for ways to modify those responses and to determine the optimal timing and anatomic location for therapeutic interventions. In the case of acute myocardial infarction, caused by sudden occlusion of a proximal coronary artery, decisions about the appropriate intervention, its timing, and its anatomic location are usually quite clear. But in patients with stable or intermediate coronary syndromes, for whom prevention of future coronary occlusion is a primary goal, the optimal targets may be less clear. These patients usually have multiple atherosclerotic loci of varying bulk and metabolic activity. Identification of appropriate targets for direct intervention revolves, to a degree, around the following question: Are the inflammatory responses of the atherosclerotic process inherently an adaptive response to vascular injury? More specifically, does progression to “mature” plaque signal reduction of the threat of sudden coronary occlusion? If the answer is yes, then interventions might be directed at hastening or augmenting the plaque maturation process by using mechanical or biological interventions, or both. Conversely, if we find that atherosclerosis is a progressively malicious process, interventions might more appropriately be directed at arresting the natural progression of events.

In the past decade or so, cardiologists have acquired an intriguing assortment of tools for the diagnosis and treatment of coronary artery disease. Electron beam CT (EBCT) is a minimally invasive imaging modality that affords the study of vast numbers of patients and asymptomatic subjects. This technique provides quantitative assessment of mature coronary plaque, in the form of coronary calcification. Some studies have shown that EBCT-detected coronary calcium is an extremely powerful predictor of future coronary events in symptomatic and asymptomatic populations. These studies indicate that abundant mature coronary plaque is at least a risk factor for clinical events and, possibly, is a cause of those events. However, other studies have shown that a significant minority of patients with acute coronary syndromes have little or no EBCT-detectable coronary calcium. In addition, EBCT does not appear to be highly predictive of the anatomic location of future cardiac events. Doubts about the causal role of mature coronary plaque are supported by postmortem studies in a few patients, which indicate that lethal coronary occlusion frequently occurs at the site of an immature lipid-laden plaque. Resolution of this apparent paradox may ultimately come with recognition that abundant mature coronary plaque is an epiphenomenon, heralding the presence of radiographically silent, but extremely dangerous, unstable atherosclerotic plaque.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Beckman et al use another recently developed diagnostic tool, intravascular ultrasound imaging (IVUS), to address the question of whether plaque calcification is a protective or malignant process in the setting of existent coronary atherosclerosis. The investigators quantified the amount of calcium present in the culprit lesions of patients with symptomatic coronary disease and correlated the findings with acuity of symptom presentation. The findings indicate that coronary plaque calcium is less abundant in culprit lesions in patients with acute coronary syndromes than in patients with stable angina. These findings support the hypothesis that plaque calcification affords some protection...
against acute rupture and subsequent occlusive thrombosis. By inference, these findings can be taken to suggest that infarct-prevention interventions might be most effective when they are directed at less calcified coronary lesions. Extrapolation of the findings of Beckman et al to that extent commands a note of caution. The IVUS procedure was performed in a very small fraction of patients, all of whom were already symptomatic. Analysis of plaque morphology was retrospective and did not influence decisions about mechanical intervention. Adoption of a therapeutic strategy based on IVUS determination of plaque composition will require prospective testing. Whether calcification per se stabilizes atherosclerotic plaque is subject to the same epiphenomenal challenges as EBCT. It is possible that another factor, eg, cross-linking of interstitial collagen, is the primary protective process and that calcium is present only by association.

It should be noted that the findings of Beckman et al^19^ have not been universally observed in previous studies addressing the same question. Although Hodgson et al^20^ reported similar conclusions, de Feyter et al^21^ found that culprit lesion characteristics were similar, with respect to the amount of calcium detected by IVUS, in patients with stable versus unstable clinical presentations. Abizaid et al^22^ preliminarily addressed the issue of whether IVUS-based characterization of plaque composition can be used to forecast future coronary events. Their answer, based on findings in 122 patients with moderate stenosis of the left main coronary artery, was negative. Patients who incurred coronary events in the year after index catheterization were actually found to have slightly larger arcs of calcification than did patients who did not have coronary events (P=NS). The study included “soft” end points, such as revascularization, with an overall event rate of 18%.

Despite very impressive recent advances in coronary risk factor identification and modification, heart attack remains the most common cause of death in Western societies. Most denizens of these societies who survive past 60 years of age have evidence of advanced atherosclerosis in their coronary arteries. They are at high risk of future myocardial infarction. Heart attack remains the most common cause of death in Western societies. Thus, it is apparent that for the foreseeable future, clinicians and researchers will be challenged to define optimal treatment strategies for the direct treatment of coronary atherosclerosis. Future investigations at all levels of biomedical research hold great promise toward meeting that challenge.

## References


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