EDITORIAL COMMENT

Plaque Characterization: Surrogate Markers or the Real Thing?*

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Despite what we have learned about atherosclerosis and coronary artery disease, more than 50% of cases of acute myocardial infarction still occur unexpectedly, and many of these present as sudden death (1). We understand many of the biological and environmental factors involved in the development of coronary artery disease and even have appreciated recently that certain time-honored risk factors (hypertension, smoking, diabetes, hyperlipidemia) are present in the majority of cases, which can serve as general signposts of its presence (2). We also recognize the potential of certain drugs (such as aspirin, statins) to alter the natural history of the disease by postponing clinical sequelae.

Nevertheless, it is likely that acute coronary syndromes will continue to increase as the population at risk expands and ages, despite the enormous strides made in preserving life and reducing morbidity after an event. Coronary artery disease is a chronic but mostly silent condition that appears unlikely to be cured in the classical sense. If we are ultimately to shift from an era of secondary prevention to one of primary prevention, other tools will be needed to define risk.

One key question to answer is: can we assess the risk of acute myocardial infarction within a specified time frame for an individual patient? For patients harboring clinically occult disease, this conundrum must be solved before we can design clinical trials focused on treating the insidious vulnerable or unstable plaque because such trials otherwise might be preemptively expensive if based solely on “hard” outcomes like death or infarction. We will need to define and validate new risk factors, such as lesion anatomy, composition, chemistry, and metabolism, which apply to individuals rather than to statistical amalgams of patients. We will need to sample the “state” of the vasculature more precisely at specific moments in time and space. And of course, we would like to do all of this noninvasively, repeatedly, and conveniently so we can verify the efficacy of our interventions!

In response to these needs, a number of laboratories have accepted the challenge of molecular characterization of the vulnerable or unstable portion of the plaque. The era of noninvasive molecular imaging and targeted therapeutics has just begun for diagnostic cardiovascular imaging and is poised to facilitate a transition to more preventative strategies. These new tools detect not just the mere existence of disease but quantitatively delineate the causative molecular constituents of disease in time and space (3,4). Novel targeted contrast agents are being developed for plaque characterization (5). For example, unstable lesions might be detected with the use of targeted contrast agents that identify fibrin deposited within plaque microfissures (6), adhesion or thrombogenic molecules expressed on endothelium of vulnerable plaques (7–11), matrix metalloproteinases in the cores of progressing lesions (12), or even early angiogenic expansion of the vasa vasorum that supports plaque development (13).

Recent efforts in morphologic plaque characterization have taken advantage of technical innovations in the arenas of computed tomography and magnetic resonance imaging (14). These developments follow a long history of ultrasound tissue characterization studies aimed at defining lesion components based on signal processing of raw radiofrequency backscatter data (15). For example, ultrasound has been shown to identify lesion calcification, lipid content, plaque cap integrity, as well as to provide more traditional surrogate measures of disease activity such as carotid artery intimal-medial thickness (16).

The clinical adoption of any of these approaches to risk stratification of individual lesions depends in large part on the ultimate therapeutic consequences of having such information. Although our existing diagnostic tests, such as nuclear or echo imaging stress tests, can detect flow-limiting obstructions, they convey no direct information about plaque biology. Even invasive cardiac catheterization provides no useful information on the biological activity of plaque. Thus, as we tiptoe into the molecular imaging arena, the quest continues to define new noninvasive surrogate measures of coronary disease based on characterizing atherosclerotic burden elsewhere in the body.

The report by Honda et al. (17) in this issue of the Journal describes progress in ultrasonic interrogation of atherosclerosis, which has emerged out of the historical context of classical quantitative tissue characterization work (18). The thrust of the work is to determine whether carotid ultrasound can be used as a surrogate marker to predict acute coronary artery syndromes. The methods used in the study entail quantification of the energy of ultrasound backscattered from selected regions of vascular tissue, which is managed automatically with a special kind of signal processor that yields an quantitative index known as integrated backscatter (IB) (19,20). The magnitude of IB is governed in part by the material properties of the tissue in question (e.g., density, compressibility) (21). Accordingly, image contrast is provided by tissue components with very different
physical characteristics, such as fat, collagen, or calcium, which each manifest increasing levels of IB in rank order. Because fatty lesions generally are regarded as both more vulnerable to rupture and more thrombogenic than are fibrous ones, the propensity to acute coronary syndromes might be estimated with ultrasound if levels of IB could discriminate quantitatively among these various plaque components.

The major observations in the present study are that: 1) patients with acute coronary syndromes had carotid plaques with lower IB than those without such syndromes (i.e., they have more fatty plaques); 2) the presence of “low IB plaques” predicted more complex coronary lesions (as defined by cardiac catheterization) and more coronary events; and 3) low IB plaques were independent predictors of bad outcomes from coronary disease, irrespective of other risk factors. Although it is well known that intimal-medial thickness can be used as a surrogate for diffuse atherosclerosis and for monitoring the response to cholesterol lowering therapy (22), the present trial shows that quantifiably vulnerable plaques segregate together in various vascular territories and auger bad responses in general. These data confirm and extend similar earlier work by Takiushi et al (23), who studied patients with carotid artery disease and observed low levels of IB (i.e., fatty lesions) in carotid arteries of patients at high risk for myocardial infarction.

A long history of quantitative ultrasound vascular tissue characterization aids interpretation of these conclusions. Early work by Barzilai et al. (24) identified vascular calcification as a source of high IB and high acoustic attenuation. Others also have pioneered similar methods to differentiate fatty from fibrous tissues with quantitative backscatter in vitro (25). For example, IB can be used to infer changes in plaque composition from fatty to fibrous tissues with quantitative backscatter in vitro (25). For example, IB can be used to infer changes in plaque composition from fatty to fibrous tissues that follows cholesterol lowering (e.g., 10-fold increase in IB without any change in plaque dimension) (26). More recent studies with clinical ultrasound instruments have pursued similar methods to show that carotid and coronary artery plaques can be classified as fibrous or fatty with the use of quantitative tissue characterization methods (23,27). Thus, another justification for clinical application of these techniques is that we may be able to quantify plaque “regression” in individual patients.

What remains to be seen is where such techniques fit within the expanding panoply of noninvasive imaging methods for plaque characterization, or even among other more general serum markers of risk, such as C-reactive protein, Lp(a), fibrinogen, and the like. A strong commendation for ultrasound is that it is already employed routinely in vascular laboratories throughout the world for detection of carotid stenoses. It is cheap, simple to perform, well tolerated by patients, and can have direct therapeutic consequences (endarterectomy) if a positive interpretation is rendered.

The quantitative ultrasound measures proposed by Honda et al. (17) could be implemented on any existing equipment with modest effort on the part of manufacturers so that a clinical trial of sufficient power could be conducted to decide whether this measurement is worth touting as a noninvasive screening test for vulnerable coronary plaque. The ease of acquiring quantitative information about plaque structure and composition could be a boon for the noninvasive longitudinal evaluation of therapies designed to stabilize lesions by converting them from the vulnerable fatty stage to a more stable fibrous composition. Such methods may find complementary usage in the molecular imaging era where both the mechanisms and the local outcomes of disease (e.g., plaque composition and morphology) could be defined with greater precision to improve decision making for individual patients.

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