EDITORIAL COMMENT

Coronary Artery Calcification and Myocardial Perfusion

Kissing Cousins or Distant Relatives?*

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Cardiologists have more tests, gadgets, and cures than we know what to do with. We can visualize coronary anatomy invasively and soon noninvasively. We can assess ischemia with electrocardiograms, radionuclides, echocardiograms, and magnetic resonance imaging. We can measure the temperatures of plaques and peer into atherosclerotic-laden arterial walls. We even talk to and examine patients.

With all of our tests and gadgets, we still do not precisely know who is going to experience cardiovascular events and when they will occur. Surveying risk factors helps, but they only provide us with rough estimates. The majority of patients suffering a myocardial infarction would not qualify for cholesterol lowering the day before based on current guidelines. We urgently need to move from “target lesions” to “target patients.” Electron beam and multidetector tomography have enabled us to measure coronary artery calcification (CAC) with an ease and accuracy that was never possible for those of us who grew up with only fluoroscopy. The question is what does CAC mean? Who needs CAC assessed? How should cardiologists treat patients with very low or very high scores? These are fundamental questions for how we manage the epidemic of heart disease.

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In this issue of the Journal, Wang et al. (1) report a close correlation between CAC and myocardial perfusion reserve in 222 men and women assessed with adenosine-induced hyperemia and magnetic resonance imaging. The subjects were asymptomatic participants in the 6-center MESA (Multi-Ethnic Study of Atherosclerosis), which is attempting to place several traditional and evolving markers of coronary atherosclerosis into prognostic perspective (2). Patients were divided into the following CAC groups using the Agatston score approach: 0, 1 to 99, 100 to 399, and ≥400. Overall, perfusion reserve was monotonically lower across the increasing CAC levels. A CAC score ≥400 was associated with an odds ratio 5 times higher for decreased perfusion reserve compared with a 0 score. Importantly, adjustment for the traditional Framingham risk factors did not substantially modify this association, but it was attenuated in older subjects (65 to 84 years of age) and to some extent in women. This study supports the findings of prior studies, including a single-center investigation of 411 mostly asymptomatic patients evaluated with electron beam computed tomography and single-photon emission computed tomography (3). In this prior study, no patient with a CAC score <10 had stress-induced ischemia, whereas 46% of those with a CAC score ≥400 had demonstrable ischemia.

What questions does this study answer? Since introduction, the meaning and clinical value of CAC have been highly controversial. The overzealous marketing accompanying its early use gave the technique a black eye. With time and the increased access afforded by multidetector scanning, its acceptance as a legitimate test has grown. A revised American College of Cardiology Clinical Expert Consensus Document on CAC is almost finished and will be published this spring. The current study confirms that CAC is both anatomically and physiologically relevant, especially in middle-aged men. It is more than a rough marker of global atherosclerosis burden.

Whatever the technology, we need a screening test to tell us who is at risk for a cardiovascular event and what therapies are appropriate. In our self-imposed silos, invasive cardiologists only feel comfortable with visualization of coronary anatomy and preventive cardiologists are content with knowing only the risk factor substrate. Each of us has a special hammer and is looking for just the right nail that may or may not put the patient back together. Neither of these approaches makes total sense. We do not need to find lesions in asymptomatic patients that are not going to rupture. This limitation of the anatomist’s viewpoint needs to be addressed before we are able to assess everyone’s coronary anatomy thanks to computed tomographic angiography, followed immediately by stenting every bump in sight. Even as a preventive cardiologist, I know that many of my healthy patients will not benefit from the intensive risk factor modification they are receiving. My mother died at age 96 without any evidence of cardiovascular disease, but with an untreated cholesterol value of 350 mg/dl. She obviously did not need treatment. We need to focus on the fundamental question, who is at risk and who needs treatment?

Coronary perfusion indexes, such as stress-induced ischemia and perfusion reserve, provide that advantage. We once thought that these indexes simply measure the severity of upstream stenoses. Even at that time, this concept did not make complete sense because we knew that similar-grade stenoses produced very different consequences to perfusion reserve (4). We now know that functional indexes also reflect coronary endothelial function and microvessel disease, both of which correlate with ongoing atherosclerotic activity (5). Atherosclerotic activity is closer to our goal of

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knowing who will have an event. Even nonlocalizing measures of inflammation and endothelial dysfunction seem to provide prognostic information (6,7). Numerous clinical trials support the concept that patients with demonstrable myocardial ischemia are at increased risk and derive greater benefit from coronary intervention (8).

Clearly, CAC occurs only in the setting of atherosclerosis. It does not correlate closely with stenosis severity, but probably is a better index of global atherosclerotic burden. For patient prognosis, this is an advantage because disease burden rather than stenosis severity predicts outcome.

The present report suggests that CAC may be an appropriate screen for a true cross-section of the population. Prior studies were generally limited to selected cohorts. It confirms that CAC measures more than atherosclerosis, namely its associated functional impairment. This capacity and its ability to assess global disease burden may be the major reasons why CAC adds independent prognostic information in almost every study to date (9). This present study places reservations on CAC as a prognostic marker in older and possibly female patients, which supports our existing understanding.

Some details of this report deserve comment. The largest intergroup difference in perfusion reserve in middle-aged subjects is between those with scores 100 to 399 and ≥400. Very high scores are associated with considerable functional impairment. This finding suggests that very high CAC scores carry the greatest independent prognostic relevance, as has been observed in outcome trials (10). At the other end of the CAC spectrum, there is also considerable difference in perfusion reserve between those with 0 and low scores. Whether this observation correctly implies that we can withhold therapy from those middle-aged patients with no CAC is a critical question, but one beyond the scope of this study.

The present study does not answer our ultimate questions. We will have to wait for the completion of the MESA trial to learn how good CAC really is as a population screening test for actual coronary risk, especially compared with the myriad traditional and evolving risk markers, which are also being investigated. The study tells us nothing about how we should treat a patient with absent, medium, or high CAC scores. Because it did not include subjects under 45 years old, it cannot tell us when we might wish to start assessing CAC. Finally, the paper reports that left anterior descending CAC is related to segmental perfusion reserve, but does not provide the actual data. This regional association hints that CAC may predict the need for specific artery intervention. If confirmed, this would certainly take CAC to a level beyond that of a much-maligned rough global screen. Despite limitations, this article is a meaningful step forward and tells us that CAC may be more than an economically rewarding curiosity. It may be of real value as a coronary screen in appropriate populations.

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REFERENCES