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Editorial

Coronary calcium scoring: What does it really mean?

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Coronary artery calcification (CAC) is an active cellular process similar to bone mineralization that is an integral part of the atherosclerotic process. CAC has been shown to correlate with the overall extent of coronary artery disease as measured by luminal stenosis in autopsied hearts but shows only a moderate correlation on a segment-by-segment basis.[1] This histologic discrepancy has been attributed to an increase in coronary artery diameter resulting from remodeling of the supporting wall without encroachment into the lumen as plaque burden increases. Thus high calcium deposition may occur in the wall of the vessel without intruding into or narrowing the lumen and causing a reduction in the cross-sectional area. Such lesions may not limit coronary artery blood flow sufficiently to cause exertional chest pain, perfusion defects on stress myocardial perfusion imaging, or wall motion abnormalities on stress echocardiography. However, in asymptomatic individuals these calcium-containing noncritical atherosclerotic plaques are at risk for rupturing and causing myocardial infarction and sudden cardiac death.

Those of us involved in nuclear cardiology who are strong advocates of the prognostic value of

our techniques may not be as good as we think but just plain lucky. That is, the presence of the obstructive high-grade lesions that we see on our perfusion images is usually associated with a very large number of nonobstructive vulnerable plaques that put patients with strong positive scans at risk for major adverse cardiac events. We do not see these lesions. Thus individuals with a normal perfusion study and a less than 1% yearly event rate still have vulnerable plaques present but in much smaller numbers than those individuals with the critical stenosis that we identify. It will be extremely important for nuclear cardiology to develop some method to identify these vulnerable plaques in the near future. Advocates of electron beam computed tomography (EBCT) believe that the real role of calcium scoring is to identify such individuals so that they can be aggressively treated to prevent cardiac death or a myocardial infarction as the first manifestation of coronary artery disease.

The relationship between CAC, measured by cine fluoroscopy, noninvasive testing, and coronary artery disease in asymptomatic individuals was described in the late 1970s.[2] With the development of EBCT in 1984, more precise measurements of CAC became possible. Because EBCT systems have had a limited clinical application and were not widely available, the recent development of multidetector computed tomography (CT) (MDCT) has made such measurements more readily available. Despite this long experience, the optimal utilization of CAC for diagnosis and management of coronary artery disease remains one of the most controversial areas in clinical cardiology, especially as a screening tool in asymptomatic individuals.[3,4] This controversy is the result, in part, of a lack of clinical data, direct mass marketing to the public, and a lack of payer reimbursement.

Unfortunately, the article by Moser et al[5] in the current issue of the journal does not begin to settle all of the controversies in the field. It does address three important major issues: the relationship between CAC and conventional cardiac risk factors; the relationship between CAC and single photon emission computed tomography (SPECT) myocardial perfusion imaging, and the reproducibility or variability of MDCT measurements. For these reasons, it is making a contribution to the field and helping to define the role of nuclear cardiology.

How much does CAC add over conventional cardiac risk factors for identification of asymptomatic individuals at high risk for major adverse cardiac events?

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There are several well-recognized models that use clinical risk factors to predict hard cardiac events in asymptomatic individuals.[6,7] Although these risk factor models do a good job overall, there are limitations, especially in special populations, and the use of noninvasive testing has been suggested as a method of improving and simplifying the risk stratification process for hard cardiac events.[8] CAC as measured by EBCT has been shown to add incremental value over these variables.[9] However, in asymptomatic populations of very high-risk individuals, neither risk factor assessment nor CAC measured by EBCT was found to be an accurate predictor of cardiac events.[10] In this patient group EBCT did not add significant incremental information to risk factors. It was concluded that the use of CAC for clinical screening in this population was not justified. Needless to say, this issue has not been resolved, and the 6000 asymptomatic individuals enrolled in the ongoing National Institutes of Health/National Heart, Lung, and Blood Institute's MESA study using EBCT measurements of CAC will provide answers in a few years.

The work of Moser et al using MDCT found a linear relationship between the number of cardiac risk factors and CAC score. More than 25% of individuals with 3 or more risk factors had a score greater than 100 consistent with moderate to severe CAC. Although 33% of individuals with 1 or 2 risk factors also had some degree of calcification, only 10% had moderate to severe calcification. These results support the correlation between CAC measured by MDCT and traditional cardiac

risk factors in asymptomatic individuals as has been demonstrated with the use of EBCT. The authors concluded that MDCT screening is most useful in asymptomatic individuals with 3 or more risk factors, as the probability of finding a high-risk CAC is increased relative to individuals with only 1 or 2 risk factors. Although the current publication does not look at prognosis, the good agreement between risk factors and CAC suggests that there will be a relationship. The mantra for the ongoing quest to practice evidence-based medicine is again invoked: large clinical studies are needed using MDCT to demonstrate a direct relationship with prognosis.

How does knowledge of CAC influence management?

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A frequently asked question is as follows: What is the relationship between the observed CAC in an asymptomatic individual and the need to do further diagnostic testing? There is universal agreement that aggressive risk factor reduction by medical measures is indicated in all patients sent for screening. The question that remains is when a patient with an abnormal EBCT study should be sent for a noninvasive imaging study such as stress myocardial perfusion imaging or echocardiography versus direct referral to coronary angiography. Are there cutoffs? In a very well-done study by He et al,[11] they identified 3895 predominately asymptomatic patients with CAC by EBCT. Of these, 411 were clinically referred for myocardial SPECT perfusion imaging within a median of 17 days. The mean CAC for the entire group was 440 ± 640 and ranged from 0 to 4611. All individuals with a CAC of 10 or less had normal perfusion SPECT studies. As the CAC increased, there was an increase in the percentage of patients with positive SPECT studies: CAC of 11 to 100, 2.6%; CAC of 101 to 399, 11.3%; and CAC greater than 400, 47%. Thus patients with CAC greater than 400 should, at a minimum, be referred for further diagnostic imaging studies, as there is a 47% chance that they will have a positive SPECT imaging study. Direct referral to coronary arteriography is not indicated because in the 47% with positive studies, only a small percentage had a high-risk imaging study that might benefit from further referral for coronary arteriography.

The importance of this linear relationship between CAC and outcomes has been shown by Raggi et al[12] using EBCT to measure coronary calcium in 632 asymptomatic patients and following them up for a mean of 32 ± 7 months for the occurrence of sudden death or nonfatal myocardial infarction. They found a linear relationship between CAC and the yearly major adverse event rate: a rate of 0.11% for a score of 0, 2.1% for a score of 1 to 99, 4.1% for a score of 100 to 400, and 4.8% for a score greater than 400. This and subsequent studies helped to establish the ranges for CAC scoring that have been proposed to separate patients into risk categories for major adverse cardiac events. The generally agreed upon CAC and risk levels for nonfatal myocardial infarction and sudden death are as follows: 0 to 10, low risk; 11 to 100, moderate risk; 101 to 400, high risk; and 401 or greater, very high risk.[13] The current study by Moser et al using MDCT supports the relationship between CAC measured by EBCT and SPECT perfusion imaging demonstrated by He et al[11] in patients with CAC greater than 400, but in the intermediate groups, there was no agreement. However, only 102 of 794 patients with CAC scoring were referred for SPECT, and of these, only 19 had abnormal SPECT studies. The small sample size and potential referral bias limit these conclusions, but they are in line with the prior studies.

What is the best way to measure CAC: EBCT or MDCT?

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Unlike conventional or helical CT systems, which obtain images by using a rotating x-ray source, EBCT uses a scanning electron beam capable of very rapid acquisition. This allows electrocardiography-gated acquisition of the heart with imaging speeds as fast as 50 to 100 milliseconds per image. These high speeds freeze cardiac motion during acquisition and

minimize the blurring of calcium that occurs with the much slower helical CT systems. Multiple 3-mm-thick slices are acquired in approximately 20 seconds with the patient at rest and during breath holding. The aspect that has the most appeal to patients and referring physicians is that exercise, drugs, ionic contrast, radioactive agents, and intravenous catheters are not required. One of the limitations of EBCT is that it is not optimal for whole-body imaging and cannot be used for the frequently requested conventional CT examinations. Conventional CT systems are not capable of such high temporal or spatial resolution, and CAC measurements obtained as part of whole-body scans are not reliable because of the blurring caused by cardiac motion during acquisition. The radiation dose to the patient is higher with these conventional CT systems. With the new generation of multidetector CT systems, both temporal resolution and spatial resolution are improved. In the study by Moser et al using MDCT, four 2.5-mm-thick slices were acquired with a 250-millisecond temporal resolution during a 20-second breath hold.

The major advantages offered by MDCT for measuring CAC are the lower equipment cost and ability to perform good-quality whole-body and head imaging. Because of inferior spatial resolution, EBCT systems have been limited to cardiac applications. The current study looked at the interscan variability of MDCT CAC measurements. Moser et al found that the overall variability was greater than that reported for EBCT. Within the 3 groups, the highest variability of 86% was found in individuals with minimal CAC levels (Agatston score = 1-10) in comparison to 64% to 66% as reported for EBCT. The difference was attributed to the higher temporal resolution of EBCT. In the moderate and severe groups, the overall variability decreased, and there was slightly less variability with MDCT: 15% versus 12% to 22% in individuals with moderate CAC levels and 9.5% versus 9.2% to 13% in those with severe CAC levels for MDCT and EBCT, respectively. This suggests that in individuals with intermediate- to high-risk CAC levels, serial measurements by MDCT can be used for monitoring.

It has been shown by EBCT that CAC can be used to monitor the rate of progression of coronary calcification and the benefits associated with lipid lowering.[14,15] However, the role of serial monitoring of CAC for clinical management has not been established, and there are no recommendations at this time on the benefits of such an approach.

Moser et al have shown the relationship between risk factors, SPECT studies, and CAC using MDCT and verified that this technique has good reproducibility in individuals in the intermediate and severe CAC ranges. They have not answered the fundamental questions related to the role of CAC in asymptomatic patients but have provided evidence that MDCT can be used to evaluate such individuals in much the same way we have been using EBCT. The time to abandon SPECT systems because of the impending dethronement by CAC measurements has not yet arrived.

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