Use of coronary artery calcium scanning as a triage for cardiac ischemia testing

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Early studies that compared the results of coronary fluoroscopy to autopsy findings demonstrated a strong correlation between coronary artery calcification (CAC) and the presence of coronary atherosclerosis.[1,2] Subsequent studies further demonstrated a correlation between coronary calcium and evidence of coronary artery disease (CAD) on coronary angiography.[3,4] The later advent of electron beam tomography (EBT) was a major advance in CAC scanning, due to its improved resolution and digital nature, leading to its ability to detect and quantify the amount of coronary calcification. Arthur Agatston and Warren Janowitz described what became to be known as the Agatston score, providing a quantitative variable regarding the amount of CAC that has been used clinically to this day.[5] Subsequently, modern multislice CT scanners, used ubiquitously among medical centers, made widescale CAC scanning practical. Accordingly, research into the potential clinical utilities of CAC scanning has grown exponentially, leading to recognition of strong capabilities for CAC scanning as summarized in Table 1. In the current issue of the Journal, Assante and associates report on the relationships of CAC scanning to findings on PET myocardial perfusion imaging.[6] This article provides an opportunity to explore the use of CAC scanning in patients with suspected obstructive CAD.

CAC detection by non-contrast CT scanning is nearly pathognomonic for atherosclerosis. The CAC score provides a quantitative measurement of the overall coronary atherosclerotic burden[7]—a measurement not currently available with other forms of testing, including coronary CT angiography. Related to this feature, the CAC score is a potent predictor of cardiac events—the dominant factor leading to its widespread use. The prognostic value of the CAC score has been consistently found in now hundreds of manuscripts. A zero CAC score is a reliable predictor of very low risk for cardiac events,[8,9] while event rates increase incrementally according to CAC score among those with abnormal CAC scans.[10,11] Moreover, CAC scanning provides incremental information for predicting outcomes when considering all other available clinical information. Among asymptomatic cohorts such as MESA, CAC scanning has been shown to provide strong net reclassification improvement for the prediction of cardiac events, far outweighing that provided by other potential screening tests for CAD.[12]

EXPERIENCE WITH CAC SCANNING IN STRESS TEST POPULATIONS

While widely used for risk stratification and guiding management of asymptomatic individuals, the use of CAC scanning in patients whose signs and symptoms are suggestive of CAD is less well studied. CAC scanning is highly sensitive, though non-specific, for detecting hemodynamically significant CAD. Nevertheless, the correlation between the magnitude of CAC and the likelihood of significant CAD should not be

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Table 1. Salient aspects of coronary artery calcium scanning

Its presence is pathognomonic of atherosclerosis
It is a sensitive test for detecting the presence of coronary atherosclerosis
Indirectly reflects the total burden of atherosclerosis
Proportional relationship to the magnitude of significant coronary stenosis
Potent predictor of adverse cardiac outcomes
Provides incremental prognostic information versus CAD risk factors
Provides strong net reclassification improvement
Proportional relationship to the frequency of inducible myocardial ischemia
Low radiation exposure
Inexpensive compared to other imaging tests

overlooked.[13] This correlation is useful since it means that the results of CAC scanning can be used in algorithms that are designed to estimate the likelihood of angiographic CAD.[14]

In 1979, Diamond and Forrester published their classic algorithm for estimating the Bayesian likelihood of CAD.[15] Of note, the results of coronary fluoroscopy was one of the tests foreseen by them as a means for estimating CAD likelihood in diagnostic patients.[15,16] Indeed, at the time of the study's publication, coronary fluoroscopy was being routinely employed among diagnostic patients undergoing exercise myocardial perfusion scintigraphy at Cedars-Sinai Medical Center. However, this early diagnostic use of CAC assessment did not last. Following the advent of EBT, investigators and clinicians began to exclusively focus on the potential utility of CAC scanning as a screening test for CAD, and this narrow focus has been subsequently maintained over the years. In contrast to the intense interest in applying CAC scanning for screening purposes, there has been only limited and sporadic study concerning the potential use of CAC scanning for other clinical purposes.

In 2000, He et al reported the first experience involving the performance of CAC scanning among patients undergoing stress-rest myocardial perfusion single-photon emission tomography myocardial perfusion imaging (SPECT-MPI).[17] Among 411 patients, the frequency of ischemia on SPECT-MPI was 0% for those with CAC scores <10, 2.6% for those with CAC scores between 11 and 100, 11.3% for those with CAC scores between 100 and 399, and 46% for those with CAC scores >400. In 2004, similar results were reported in large series by Berman et al, involving 1,195 patients, except for a lower frequency of ischemia among those with CAC

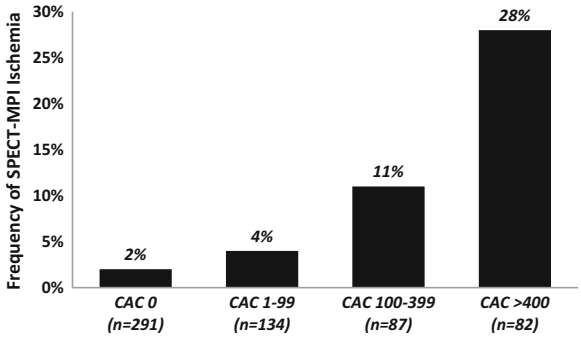

Figure 1. Frequency of ischemia during SPECT-MPI according to CAC score in the study by Assante et al.

scores >400.[18] Based on these observations, a CAC score of ≥400 became part of Appropriate Use Criteria for stress testing after CAC scanning.[19] However, despite these initially promising studies, subsequent study regarding the combination of CAC scanning and SPECT-MPI imaging has been surprisingly sparse. In fact, a recent meta-analysis of 20 studies involving CAC scanning and MPI with either SPECT or positron emission tomography (PET) found that most studies in this arena have involved only small and usually highly selected patient populations.[20] Only five of the 20 studies involved the evaluation of >500 patients.

In the current study by Assante et al, they report the relationships between CAC findings and assessments of peak myocardial blood flow and coronary flow reserve (CFR) using PET in 637 patients.[6] This relationship has only been recently and sparsely evaluated, and the present study constitutes the largest experience to-date in this regard. As noted with myocardial ischemia, significant increased frequency of reduction in CFR was noted only among patients with a CAC score >400. Thus, while CAC scoring is an anatomic test, and not a measure of physiology, per se, the findings clearly indicate a greater likelihood of important physiologic changes with increasing anatomic burden, as measured by the CAC score. Of note, as has been reported by others,[21] abnormal CFR was also not uncommon in their study in patients with CAC 0—as manifested by the wide error bars in CFR in this subgroup of their patients. This finding is consistent with the observation that CFR can be abnormal in a variety of clinical states, including diffuse, non-obstructive atherosclerosis, and microvascular disease, as well as in obstructive CAD.[22]

CAN CAC SCANNING SERVE AS A TRIAGE FOR MORE ADVANCED TESTING?

The current finding that zero and low CAC scores (i.e., score of 1-99) markedly decrease the likelihood of inducible myocardial ischemia is a reproducible finding

in the literature (Figure 1).[20] This finding, alone, suggests a strong potential role for using CAC scanning as a means of triaging which patients presenting with clinical symptoms may require more advanced cardiac testing. In addition, high CAC scores (i.e., scores ≥400) appear to signify a group with an elevated risk for ischemia, although the frequency of ischemia in patients with high CAC scores appears to vary considerably among studies.[20] Based on these findings, a rough guideline for using CAC scanning for triaging patients presenting with clinical symptoms, such as chest pain or dyspnea, is outlined in Table 2. Based on the very low likelihood of ischemia among patients with calcium scores <100, such patients may generally be referred away from more advanced cardiac stress tests. Of note however, any CAC score >0 signifies the presence of atherosclerosis, and a low absolute CAC score can still signify a high CAC percentile score in young patients, indicative of high *future* risk, even though the *present* ischemic risk is low in such patients due to the presence of only a small absolute CAC score.[18] Those with CAC scores ≥400 are at increased risk for ischemia in whom more advanced imaging testing may be indicated. Those with CAC scores that range between 100 and 399 represent an intermediate risk group.

The basic concept of using CAC scores alone to predict the likelihood of ischemia, however, does not presently include a measured consideration as to clinical factors which might alter the CAC score versus ischemia relationship. In the present study the authors addressed what factors other than CAC score might influence CFR. These factors included age, male gender, and diabetes. In a similar vein, clinical variables might be combined with the CAC score to better predict the likelihood of myocardial ischemia, particularly relevant for those patients who fall into an ''intermediate'' likelihood of ischemia based on the CAC score alone (i.e., scores of 100-399). Research in this regard, however, has been quite limited. Potential candidate variables for influencing CAC score in such patients are suggested in Figure 2. These candidate variables include gender, CAD risk factors, the presence and type of chest pain, exercise capacity, and various co-morbidities, such as those requiring the performance of pharmacologic rather than exercise stress. There are some data to support such variables in small studies. In one study, the threshold of ischemia was found to vary with the quality of patients' chest pain.[23] In a second small study, the frequency of ischemia varied according to exercise capacity among those with intermediate CAC scores.[24] In a third study, Wong et al demonstrated that among patients with a CAC score of 100-399, the frequency of ischemia was only 4% among those without concomitant diabetes or metabolic syndrome, compared to 13% among those who had diabetes or metabolic syndrome.[25] By contrast, if the CAC score was low (<100) or high (>400), the frequency of ischemia was respectively low or high regardless of the patients' metabolic status. To accommodate such investigations, future studies should include the careful collection of clinical data in large sample sizes, with careful attention to the characterization of the clinical data.

IMPLICATIONS FOR COMPARATIVE EFFECTIVENESS RESEARCH

In the current study, 84% of patients had a pre-test Bayesian likelihood of CAD that was <15% as assessed by CADENZA as described by Diamond, and the remaining 16% had an intermediate Bayesian likelihood of CAD. In the face of such low risk, current clinical guidelines would call for the use of exercise ECG as the

Table 2. Potential use of CAC scanning for triaging patients for cardiac stress testing

CAC score	Clinical management
0	There is a low likelihood of atherosclerosis and myocardial ischemia. Refer patient away from advanced imaging tests
1-99	Atherosclerosis is definitely present, but there is a low likelihood of myocardial ischemia. Refer patient away from advanced imaging tests, but initiate appropriate preventive practices due to CAC score >0
100-399	Intermediate risk for ischemia. Additional clinical information, such as presence of risk factors, chest pain symptoms, and exercise capacity may help govern the need for more advanced imaging tests
≥400	Increased risk for myocardial ischemia which may make the need for more advanced testing more likely

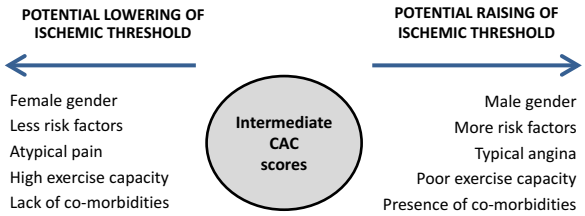

Figure 2. Candidate factors that should be evaluated in prospective study for their potential to influence the likelihood of ischemia among patients with moderately elevated CAC scores.

first diagnostic test among those who could exercise.[26] Alternatively, were CAC scanning an already accepted means for triaging such patients for cardiac stress testing, two-thirds of the patients in the present study (i.e., the 67% who had a CAC score <100), may have been spared more advanced cardiac imaging according to an algorithm that diverts patients with low CAC scores away from cardiac stress testing. Another possibility includes combining CAC scanning and exercise ECG together into a hybrid low-cost ''CAC treadmill'' test.[27] Until now, there has not been sufficient advocacy to advance the use of CAC scanning beyond its use for screening purposes. However, with increasing emphasis now being placed on providing more value-based care, particularly in an era of a declining prevalence of ischemia,[28] the time has come to evaluate the utility of CAC scanning as a guide to more informed clinical decision making when it comes to the appropriate selection of patients for cardiac stress testing.

Disclosure

None.

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