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EXPEDITED REVIEW

Relationship Between Stress-Induced Myocardial Ischemia and Atherosclerosis Measured by Coronary Calcium Tomography

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OBJECTIVES We assessed the relationship between stress-induced myocardial ischemia on myocardial perfusion single-photon emission computed tomography (MPS) and magnitude of coronary artery calcification (CAC) by X-ray tomography in patients undergoing both tests.

BACKGROUND There has been little evaluation regarding the relationship between CAC and inducible ischemia or parameters that might modify this relationship.

METHODS A total of 1,195 patients without known coronary disease, 51% asymptomatic, underwent stress MPS and CAC tomography within 7.2 ± 44.8 days. The frequency of ischemia by MPS was compared to the magnitude of CAC abnormality.

RESULTS Among 76 patients with ischemic MPS, the CAC scores were >0 in 95%, ≥100 in 88%, and ≥400 in 68%. Of 1,119 normal MPS patients, CAC scores were >0, ≥100, and ≥400 in 78%, 56%, and 31%, respectively. The frequency of ischemic MPS was <2% with CAC scores <100 and increased progressively with CAC ≥100 (p for trend <0.0001). Patients with symptoms with CAC scores ≥400 had increased likelihood of MPS ischemia versus those without symptoms (p = 0.025). Absolute rather than percentile CAC score was the most potent predictor of MPS ischemia by multivariable analysis. Importantly, 56% of patients with normal MPS had CAC scores ≥100.

CONCLUSIONS Ischemic MPS is associated with a high likelihood of subclinical atherosclerosis by CAC, but is rarely seen for CAC scores <100. In most patients, low CAC scores appear to obviate the need for subsequent noninvasive testing. Normal MPS patients, however, frequently have extensive atherosclerosis by CAC criteria. These findings imply a potential role for applying CAC screening *after* MPS among patients manifesting normal MPS. (J Am Coll Cardiol 2004;44:923–30) © 2004 by the American College of Cardiology Foundation

An increasing body of literature demonstrates that measurement of coronary artery calcification (CAC) by X-ray computed tomography (CT), using either electron beam computed tomography (EBCT) or multislice spiral computed tomograpy (MSCT), represents a potent means for improving the diagnostic assessment and risk stratification of patients with suspected coronary artery disease (CAD) (1–10). Hence, the applications of this newer technology may overlap some of the clinical applications associated with noninvasive stress tests. For instance, for nearly three decades, stress myocardial perfusion single-photon emission computed tomography (MPS) has been widely utilized for detecting CAD in patients with an intermediate likelihood of this condition, and for nearly as long it has been established as highly effective for risk stratification of patients with an intermediate or high likelihood of CAD (11–19). Thus, stress MPS is now commonly used for shaping key clinical management decisions among patients with suspected or known CAD, such as distinguishing which CAD patients are likely to benefit from coronary revascularization versus medical management (20). The wide use and ubiquitous presence of noninvasive stress tests, such as MPS, coupled with the increasingly recognized utility and growing availability of CAC scanning, raises a new clinical problem for clinicians: how should CAC scanning be integrated with conventional stress imaging tests into the clinical assessment of patients with suspected and known CAD? Understanding the potential predictive relationship between CAC levels and the likelihood of stress-induced myocardial ischemia would be central to addressing this question. Thus, we undertook the present study to examine the potential inter-relationship between the presence and magnitude of CAC and the presence and magnitude of inducible myocardial ischemia during stress MPS.

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Abbreviations and Acronyms

CAC	= coronary artery calcium
CAD	= coronary artery disease
CT	= computed tomography
EBCT	= electron beam computed tomography
HU	= Hounsfield units
MPS	= myocardial perfusion single-photon emission computed tomography
MSCT	= multislice spiral computed tomography
SDS	= summed difference score
SPECT	= single-photon emission computed tomography
SRS	= summed rest score
SSS	= summed stress score
Tc	= technetium
Tl	= thallium

METHODS

We evaluated 1,195 patients who underwent rest/stress dual isotope MPS and CAC scanning by EBCT (Imatron C-150 or GE e-Speed, GE-Imatron Inc., South San Francisco, California) or MSCT (Siemens Volume Zoom, Siemens Medical Systems, Forchheim, Germany) at Cedars-Sinai Medical Center within six months of each other (7.2 ± 44.8 days). The mean age of the study population was 58.4 ± 10.3 years, and 869 (72.7 %) of the patients were male. Patients underwent MPS on a clinical basis, and CAC imaging was performed either on a basis of self-referral (n = 94 patients), physician-referral (n = 777 patients), or ongoing research (n = 324 patients) in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study. Exclusion criteria included prior coronary bypass surgery or percutaneous coronary intervention, history of myocardial infarction, known valvular heart disease, or primary cardiomyopathy. This research was approved by the Cedars-Sinai Medical Center Institutional Review Board.

Imaging and stress protocol. Patients were injected intravenously at rest with thallium-201 (Tl-201) (3.0 to 4.5 mCi) with dose variation based on patient weight. Rest Tl-201 SPECT was initiated 10 min after injection of the radionuclide (21).

Exercise MPS protocol. Following rest MPS, symptom-limited Bruce protocol treadmill exercise testing was performed in 1,049 (88%) of the 1,195 study subjects. Exercise end-points included physical exhaustion, severe angina, sustained ventricular tachycardia, hemodynamically significant supraventricular dysrhythmias, or exertional hypotension. In accordance with our policy to discontinue anti-ischemic medications before exercise testing, only 36 subjects (3.0%) were on beta-blocking medication <48 h, 10 (0.8%) were on calcium blockers <24 h, and 3 (0.3%) were on nitrates <6 h before MPS. At near-maximal exercise, technetium-99m (Tc-99m) sestamibi (25 to 40 mCi) was injected (actual patient dose varied with patient weight) and exercise continued for an additional 1 min after injection at peak workload, and an additional 1 to 2 min at reduced workload. Tc-99m sestamibi MPS imaging was begun 15 to 30 min after radioisotope injection (21).

Adenosine MPS protocol. In 146 (12%) of the study subjects, adenosine stress was performed (22). Patients were instructed not to consume caffeine products for 24 h before MPS. Following rest MPS, adenosine was infused (140 μg/kg/min for 5 to 6 min), and Tc-99m sestamibi was injected at the end of the 2nd or 3rd min of infusion for the 5- and 6-min infusions, respectively. In patients who could tolerate it, low-level treadmill exercise, as an adjunct to adenosine infusion, was performed at 0% to 10% grade, at 1 to 1.7 miles/h. The Tc-99m sestamibi MPS was initiated approximately 60 min after the end of adenosine infusion in patients who did not exercise and 15 to 60 min after injection in those with adjunctive exercise.

During both types of stress, blood pressure was recorded at rest, at the end of each stress stage, and at peak stress. Maximal ST-segment change was assessed as horizontal, upsloping, or downsloping, and electrocardiographic ischemia was defined as ST-segments ≥1 mm horizontal or downsloping or ≥1.5 mm upsloping at 80 ms after the J point.

SPECT acquisition protocol. The MPS studies were performed on multidetector scintillation cameras using an elliptical 180° acquisition for 60 to 64 projections at 20 s per projection (21). For Tl-201, two energy windows were used, including a 30% window centered on the 68- to 80-keV peak and a 10% window centered on the 167 keV peak. For Tc-99m sestamibi, a 15% window centered on the 140-keV peak was used, and images were obtained in both supine and prone positions. For supine rest and stress MPS studies, gated SPECT was performed, obtaining 8 to 16 frames/cycle. Images were acquired using a 64 × 64 image matrix and were subject to quality control measures as previously described (21). No attenuation or scatter correction was employed.

Interpretation of SPECT. Semiquantitative visual interpretation was performed using 20 segments for each image set. Segments were scored by consensus of two experienced observers using a 5-point score (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = absence of detectable tracer uptake in a segment) (21).

Scintigraphic indices. The summed stress score (SSS) and summed rest score (SRS) were obtained by adding the scores of the 20 segments of the respective images (19). An SSS ≥4 was considered abnormal (21). The sum of the differences between each of the 20 segments from these images was defined as the summed difference score (SDS), incorporating assessment of both the extent and severity of stress-induced myocardial ischemia, each of which independently adds prognostic information (11). The SDS was converted to percent myocardium ischemic by dividing the SDS by 80—maximum potential score (4 × 20)—and multiplying by 100. Ischemic and moderate-to-severe ischemic MPS studies were defined by ≥5% and >10% of the myocardium, respectively (20). Because the presence and magnitude of hypoperfusion induced during adenosine MPS is roughly equivalent to the magnitude of ischemia

induced during maximal exercise (23–27), we employ the term "inducible ischemia" to represent both the ischemia during exercise and adenosine MPS, even though stress actual ischemia is often not produced by the adenosine.

Calcium scanning. The imaging protocol involved acquiring a single scan on each patient, consisting of approximately 30 to 40 3- or 2.5-mm slices for EBCT and MSCT respectively, sufficient to cover the entire heart, with triggering at 50% to 80% of the cardiac cycle. Breath-holding instructions were given to minimize misregistration.

CALCIUM SCAN INTERPRETATION. Foci of CAC were identified by an experienced radiographic technologist and scored using semiautomatic commercial software on a NetraMD workstation (ScImage, Los Altos, California) by detection of at least three contiguous pixels (voxel size = 1.03 mm^3) of peak density ≥130 Hounsfield units (HU) within a coronary artery. Scoring was performed and verified by an experienced imaging cardiologist. The software calculated lesion-specific scores as the product of the area of each calcified focus and peak CT number (scored as 1 if 131 to 199 HU, 2 if 200 to 299 HU, 3 if 300 to 399 HU, and 4 if 400 HU or greater) according to the Agatston method (28). These were summed across all lesions identified within left main, left anterior descending, left circumflex, and right coronary arteries to provide arterial-specific calcium scores, and across arteries to provide the total CAC score that was used as the principal EBCT/CT measurements in this study. The CAC percentile score based on age and gender was assigned based on cut points from a large database of Raggi et al. (4) programmed into the ScImage calcium scoring software.

Historical and other clinical variables. Each patient was questioned regarding the following: chest symptoms, divided into four chest pain categories (asymptomatic, nonanginal chest pain, atypical, and typical angina) (29); the presence or absence of shortness of breath; medication use; and the following historical coronary risk factors: 1) family history of early coronary heart disease (male primary relative <55 years of age, female <65 years of age); 2) diabetes; 3) hypertension; 4) high serum cholesterol level; and 5) current or past usage of cigarettes. Weight and height were measured with body mass index calculated as weight (kg)/height m^2. Bayesian analyses of patient age, gender, symptoms, risk factors, and, in the exercise cohort, exercise electrocardiography results were used to calculate the pre-MPS likelihood of CAD according to a computer program (CADENZA) (30).

Statistical analyses. Total calcium scores were classified into six categories: 0 (calcium absent); 1 to 9 (minimal); 10 to 99; 100 to 399; 400 to 999; and ≥1,000 (5). When being analyzed as a continuous variable, a log transform of CAC was used to reduce the amount of skew of CAC scores and allow for multivariable statistical analyses that are based on the assumption of normality. The prevalences of an ischemic and moderate to severe ischemic MPS were compared across calcium score categories using the chi-square test of trend. These analyses were also run with stratification by gender and by presence of symptoms to examine whether relationships between CAC score category and likelihood of an ischemic MPS differed by these factors. Analyses were conducted similarly across CAC score age- and gender-adjusted percentile levels (0 to 24th, 25th to 49th, 50th to 74th, 75th to 89th, and 90th to 99th).

Moreover, among each of these percentile categories, the relation of CAC score category with MPS result was also assessed. The non-parametric Wilcoxon rank sum test for proportional variables and the Pearson chi-square test of association for categorical variables were used to compare subjects with an abnormal versus normal SPECT result. In addition, the Fisher exact test was employed when appropriate. Multiple logistic regression was performed to examine whether log (CAC score +1) was independently associated with the likelihood of an abnormal MPS result, after adjustment for standardized age, gender, presence of symptoms, other clinical characteristics, and CAD risk factors. The number of days between tests was included to control for the progression of CAD that might occur during the up to six-month interval between tests. Receiver operating characteristic (ROC) analysis was used to compare the information in predicting ischemic MPS based on age and gender; age, gender, and symptoms; and the combination of these with the CAC score. All continuous variables are expressed as mean ± SD.

RESULTS

Pertinent clinical characteristics for our study population, stratified by MPS result are shown in Table 1. Of 79 patients with an abnormal MPS, 76 (96%) also had ≥5% ischemia. The remaining 3 with abnormal MPS had SSS = 4 but <5% ischemia and were combined with the other 1,116 patients with normal MPS to constitute our normal MPS group. Compared to the patients with a normal MPS, patients with an ischemic study had a more abnormal coronary risk profile (being significantly older, with more males, more hypertension, and a higher mean pre-test likelihood of CAD) and significantly greater functional test abnormalities, including more exercise-induced chest pain, shorter exercise duration, more exercise-induced ST-segment depression, and a lower mean peak exercise heart rate. In addition, the ischemic MPS patient group manifested a significantly higher mean CAC score value versus the normal MPS patient group.

Comparison of MPS and CAC scanning. Figure 1 illustrates both the frequency of an ischemic MPS and a moderate to severe ischemic MPS, according to the absolute CAC score, grouped into six categories. Below a calcium score of 100, the frequency of an ischemic MPS was very low (<2% overall). At the other end of the spectrum, among patients with calcium scores >1,000, one-fifth had an ischemic MPS, with less than one-half of these studies (8.6% of all patients with CAC score >1,000) demonstrating moderate to severe MPS ischemia.

Comparison of the SDS by MPS versus log-transformed

Table 1. Characteristics of the Study Population

Parameter	Overall (n = 1,195)	Normal MPS (n = 1,119)*	Ischemic MPS (n = 76)	p Values
Age, yrs	58.4 ± 10.3	58.1 ± 10.2	61.9 ± 11.1	0.0028
Female	326 (27.3%)	318 (28.4%)	8 (10.5%)	0.001
Symptom class				
Asymtomatic	609 (51.0%)	572 (51.1%)	37 (48.7%)	0.681
Asymptomatic/SOB	658 (55.1%)	621 (55.5%)	37 (48.7%)	0.248
Non-anginal pain	112 (9.4%)	108 (9.7%)	4 (5.3%)	0.204
Atypical angina	380 (31.8%)	359 (32.1%)	21 (27.6%)	0.420
Typical angina	45 (3.8%)	31 (2.8%)	14 (18.4%)	<0.0001
Risk factors				
High cholesterol	897 (75.1%)	844 (75.4%)	53 (69.7%)	0.267
Hypertension	514 (43.0%)	465 (41.6%)	49 (64.5%)	<0.0001
Family history	448 (37.5%)	414 (37.0%)	34 (44.7%)	0.177
Diabetes	138 (11.6%)	126 (11.3%)	12 (15.8%)	0.232
Smoking	84 (7.0%)	78 (7.0%)	6 (7.9%)	0.760
BMI	26.9 ± 4.8	26.8 ± 4.7	27.9 ± 5.2	0.1028
CAC score	438.9 ± 703.4	388.9 ± 617.0	1,175.0 ± 1,272.0	<0.0001
Pre-rest likelihood of CAD (%)	24.4 ± 24.1	23.6 ± 23.1	36.6 ± 33.6	0.0019
Exercise stress test*	n = 1,049	n = 989	n = 58	
Ischemic stress ECG	220 (21.0%)	184 (18.6%)	36 (62.1%)	<0.0001
Exercise time	9.3 ± 2.7	9.4 ± 2.7	7.9 ± 2.8	0.0001
Exercise chest pain	83 (7.9%)	62 (6.3%)	21 (36.2%)	<0.0001
Rest HR	68.2 ± 12.2	68.3 ± 12.1	67.7 ± 13.9	0.738
Peak HR	154.3 ± 14.8	155 ± 14.4	142.1 ± 16.6	<0.0001
Rest SBP	136.7 ± 18.6	136.4 ± 18.7	142.1 ± 17.7	0.0209
Peak SBP	171.6 ± 20.7	171.8 ± 20.8	167.8 ± 18.4	0.0910
Rest DBP	80.4 ± 9.3	80.3 ± 9.2	83.3 ± 9.6	0.0250
Peak DBP	77.2 ± 9.7	77.0 ± 9.6	81.0 ± 10.9	0.0017

*Adenosine stress excluded.

BMI = body mass index; CAC = coronary artery calcium; CAD = coronary artery disease; HR = heart rate; MPS = myocardial perfusion single-photon emission computed tomography; SBP = systolic blood pressure; SOB = shortness of breath.

CAC scores revealed a significant but only fair Spearman correlation ($r = 0.195$, $p < 0.05$). This relationship was largely governed by a wide distribution of CAC scores among patients with normal MPS, as illustrated in Figure 2. Of patients with ischemic MPS (≥5% ischemia), 88% had CAC scores ≥ 100. Importantly, 56% of the patients with normal MPS also had CAC scores ≥100.

Assessment according to CAC percentile score. Because both age and gender are known to impact CAC, we examined the relationship between the age-gender percentile CAC score and the frequency of an ischemic MPS (Fig. 3). As with the absolute CAC score, a significant overall trend existed for the frequency of MPS ischemia across CAC percentile groupings ($p < 0.0005$). For patients below the 50th percentile of CAC abnormality, the frequency of an ischemic MPS study was very low (<2%). Once patients reached the 50th percentile, the frequency of ischemic MPS was substantially increased, but it did not vary substantially among 50th to 74th, 75th to 89th, and ≥90th percentile groups.

Figure 4 demonstrates the frequency of an ischemic MPS as a function of *both* the absolute CAC score and the CAC score (for all values above a 50th percentile CAC ranking). For each of the shown CAC percentile groups, there was a

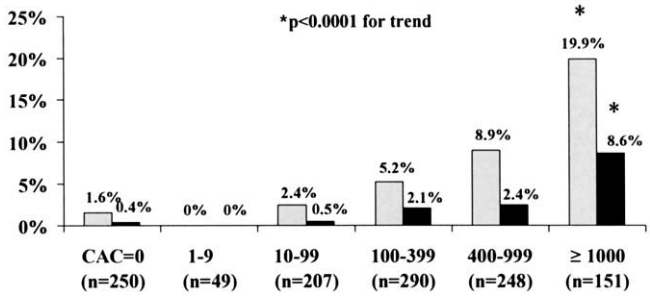

Figure 1. The frequency of an ischemic myocardial perfusion single-photon emission computed tomography (≥5% ischemic) **(gray bars)** and of a moderate to severe ischemia (>10% ischemic) **(black bars)** for patients divided into six coronary artery calcium (CAC) score groupings.

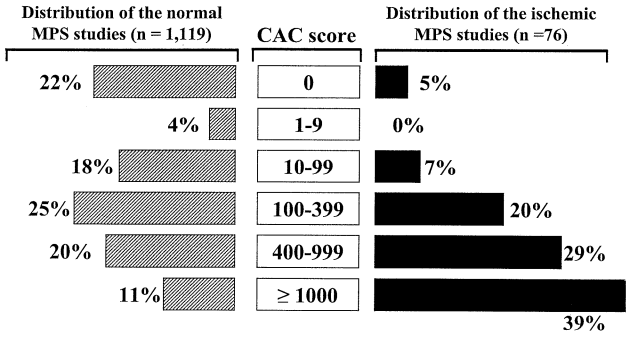

Figure 2. Distribution of coronary artery calcium (CAC) scores for the 1,119 patients manifesting a normal myocardial perfusion single-photon emission computed tomography (MPS) **(left)** and the 76 patients with an ischemic MPS **(right)**.

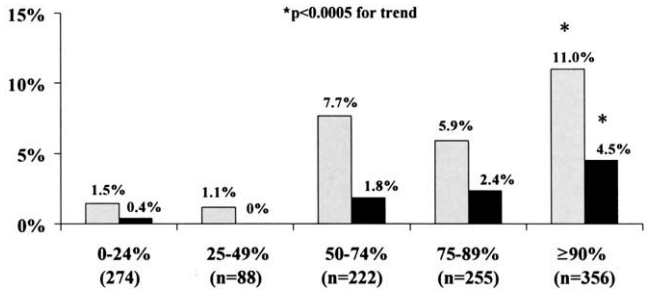

Figure 3. The frequency of an ischemic myocardial perfusion single-photon emission computed tomography (MPS) (≥5% ischemic) **(gray bars)** and moderate to severe ischemic MPS (>10% ischemic) **(black bars)** according to five groupings of age-gender adjusted coronary artery calcium percentile score.

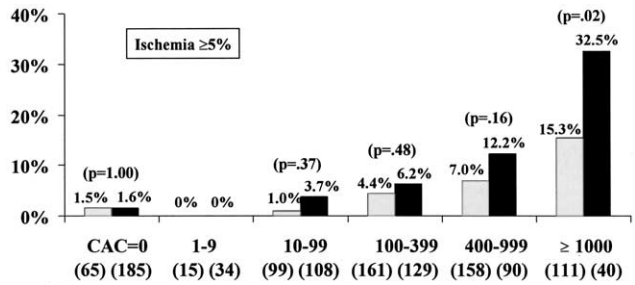

Figure 5. The frequency of an ischemic myocardial perfusion single-photon emission computed tomography for each of the six coronary artery calcium (CAC) score subgroups, further subdivided on the basis of symptoms (chest pain and/or shortness of breath) being absent **(gray bars)** or present **(black bars)**.

stepwise increase in the frequency of an ischemic SPECT study as the *absolute* CAC level increased from low to high values. Patients with a high percentile ranking (owing to relatively younger age) but low absolute CAC score did not manifest inducible ischemia during MPS.

The impact of symptoms. Dividing patients on the basis of presence or absence of symptoms altered the observed frequencies of ischemic MPS studies among patients whose calcium scores exceeded 10, as demonstrated in Figure 5. As the absolute CAC score increased, the difference in the frequency of MPS ischemia among symptomatic versus asymptomatic subjects became progressively more pronounced. When the CAC score was high (≥400), a significantly higher frequency of ischemia occurred in the symptomatic than in the asymptomatic group (18.5% vs. 10.4%; p = 0.025).

Sequence of testing. In 37.8%, 15.6%, and 46.5% of patients the nuclear scan came before, the same day, or after the CT scan, respectively. Interaction terms with test order and CAC score or category in relation to likelihood of positive MPS were nonsignificant (p > 0.05), suggesting there was no association of test order and the relation between CAC and likelihood of MPS ischemia.

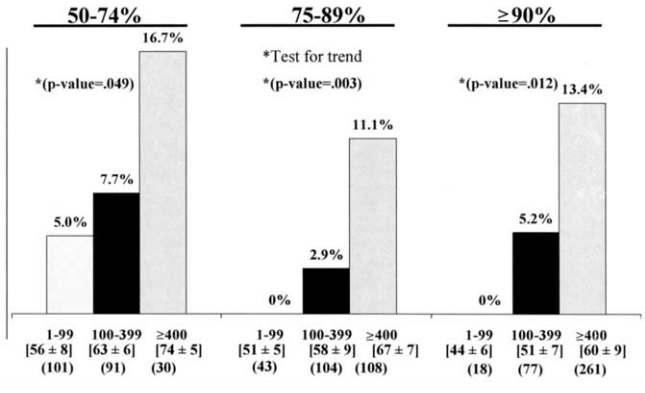

Figure 4. The frequency of an abnormal myocardial perfusion single-photon emission computed tomography (MPS) study according to coronary artery calcium (CAC) percent ranking and absolute CAC score (patients with percentile rankings <50% are not shown owing to the very low frequency of abnormal MPS studies in such patients). Within each of three CAC percentile groups, patients are further divided on the basis of their absolute CAC score, condensed into three subgroups: CAC scores of 1 to 99, 100 to 399, and ≥400. The **first set of numbers below each bar** represents the absolute CAC score; the **second set** represents the mean age ± SD; and the **third set** represents the number of patients within each of the nine subgroups that are illustrated. Note that regardless of percentile ranking, the frequency of an ischemic MPS study was relatively high when the absolute CAC score was ≥400, and relatively low when the CAC score was <100.

Multivariate predictors of abnormal MPS result. Multivariable logistic regression analysis revealed that the log CAC score was the most potent predictor of MPS ischemia in our study (Table 2). Additional significant variables included gender, the presence of symptoms (i.e., chest pain and/or shortness of breath), a history of hypertension and high cholesterol, and increased body mass index. To assess the potential incremental information provided by CAC scanning for predicting MPS ischemia, we performed an ROC analysis in which the clinical variables of age and gender were first forced into the multivariate prediction of MPS ischemia (Fig. 6). The subsequent addition of coronary risk factors and chest pain symptom information then significantly increased the size of the ROC area over age and gender from 67% to 74% (incremental p = 0.0061). Finally, the further addition of the CAC score significantly increased the resultant ROC area beyond the previous curve to 80% (incremental p = 0.0051). All three ROC curves were highly significant (p < 0.0001). Thus, the CAC score adds incremental information for predicting the likelihood

Table 2. Multivariate Predictors of a ≥5% Ischemic Myocardial Perfusion Single-Photon Emission Computed Tomography

Predictor*	Odds Ratio	p Value	95% CI
Log CAC	3.36	0.000	2.13–5.29
Age	1.18	0.260	0.88–1.59
Male gender	1.54	0.020	1.07–2.22
History of high BP	1.41	0.010	1.09–1.82
History of high cholesterol	0.72	0.009	0.57–0.92
Family history of CAD	1.34	0.026	1.04–1.73
History of diabetes	0.98	0.829	0.78–1.22
History of smoking	1.06	0.631	0.84–1.35
BMI	1.30	0.049	1.00–1.70
Symptoms	1.40	0.011	1.08–1.81
Days	0.92	0.552	0.70–1.21

BP = blood pressure; BMI = body mass index; CAC = coronary artery calcium; CI = confidence interval; CAD = coronary artery disease; Days = number of days between tests. *Predictors have been standardized.

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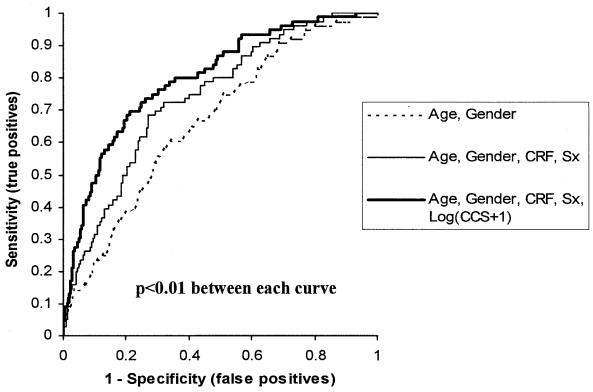

Figure 6. Receiver operating characteristic curve analysis showing incremental prognostic value of coronary artery calcium score in predicting likelihood of ≥5% ischemia. CCS = coronary calcium score; CRF = coronary risk factors; Sx = symptoms.

of MPS ischemia, even after other predictors of MPS ischemia are first considered.

DISCUSSION

Our results indicate that a threshold phenomenon governs the relationship between the extent of calcified plaque as measured by the CAC score by X-ray computed tomography and the presence of myocardial ischemia, as measured by stress MPS. When grouped according to calcium score, both patients with a relatively low and relatively high likelihood of demonstrating an ischemia MPS study could be identified. Specifically, among the patients with a calcium score <100 in our study, MPS ischemia was rare, occurring in <2% of such patients. This low frequency of ischemia with a CAC score <100 was present in patients with and without clinical symptoms, although a trend toward more ischemia in symptomatic patients with scores 10 to 99 was observed. As the CAC score increased in magnitude above 100, the frequency of myocardial ischemia on MPS increased progressively. Among patients with CAC scores exceeding 1,000, 20% manifested ischemia by MPS.

Our results further indicate that the likelihood of myocardial ischemia by MPS is more tightly related to the absolute CAC score rather than age-gender–stratified CAC percentile score. For example, among patients with CAC score exceeding 400, the frequency of myocardial ischemia was comparably high over a wide range of percentile rankings. These data indicate an important distinction. Whereas a low CAC score with a high percentile ranking in young patients may be indicative of *long-term* risk for developing cardiac events (4,6,31), this same score is probably not predictive of *short-term* risk, given the finding that most such patients have no evidence of ischemia on MPS. Thus, further testing by MPS of patients found to have high CAC percentile but a CAC score <100 would not appear to be needed in most patients. Of additional interest, our findings demonstrated that a relatively high proportion of patients referred for MPS and found to have no MPS ischemia have a CAC score ≥100, suggesting that assessment of atherosclerotic burden by CAC testing may be useful in assessing of the need for aggressive attempts to prevent coronary events.

Prior studies. Despite the apparent overlap by noninvasive stress tests (11–20) and CAC scanning (1–10) for assessing outcomes, few investigations have inquired into the interrelationship between results of stress imaging and the presence and magnitude of CAC abnormality. With one exception, the small number of prior investigations regarding myocardial ischemia and CAC abnormality primarily focused on how these indices compared in their ability to predict angiographic coronary stenoses, without direct comparison of CAC to myocardial ischemia per se (32–35). Only one prior study has specifically focused on the interrelationship between the CAC score and myocardial hypoperfusion by MPS (36). In that report, He et al. (36) noted a similar threshold phenomenon with almost no observable myocardial hypoperfusion among patients with a CAC score <100 and with a marked increase in the frequency of an abnormal MPS in patients with high CAC values. Contrasting with the study of He et al. (36), our study showed a much lower frequency of MPS abnormality among patients with CAC scores ≥400. The CAC measurements, per se, are highly standardized, and the distribution of symptoms and risk factors were not very dissimilar for these two studies. Accordingly, the observed differences in the frequency of MPS abnormality among patients with high CAC scores were most likely due to either differences in the interpretative criteria used to assess the MPS results in the two studies and/or differences in the referral pattern to MPS testing after CAC scanning. A preliminary study assessing the frequency of MPS abnormality among 121 patients with high CAC scores reported a frequency of MPS abnormality that parallels that noted in our study (37).

The impact of clinical symptoms. Most clinical studies regarding coronary artery CT have looked primarily at asymptomatic subjects. In our study, however, nearly one-half of our patients had clinical symptoms, ranging from patients complaining of shortness of breath to patients presenting with typical angina. Like the asymptomatic patients, our symptomatic patients, as a group, had a very low frequency of MPS ischemia when the CAC score was <10. But for each higher CAC score subgroup, including even patients with a CAC score of 10 to 99, the symptomatic patients manifested an approximate tripling of the frequency of MPS ischemia compared to patients without clinical symptoms. Accordingly, these results suggest that the presence of clinical symptoms is a strong modifier of the relationship between CAC scores and the likelihood of inducible ischemia once any substantial degree of CAC is present.

Multivariable analysis. The presence of coronary calcium was the most potent multivariable predictor of myocardial ischemia during MPS. In addition, chest pain, gender, and certain coronary risk factors were additional significant multivariate predictors of myocardial ischemia. Nevertheless, even when all other predictors of SPECT abnormality

were forced into a multivariate model for predicting MPS ischemia, the CAC score still added significant incremental value for this prediction. These results thus parallel prior observations indicating that CAC imaging is a potent incremental predictor for cardiac events, over and above the information provided by other known predictors of coronary events and all-cause mortality (5,6,10).

Study limitations. Most studies involving tomographic measurements of coronary calcium have been limited primarily to asymptomatic subjects or patients. Various factors have accounted for this, including the relative lack of widespread third-party reimbursement for this procedure, leading to out-of-pocket payment by largely asymptomatic patients, and the established practice of direct stress testing referral among patients with anginal symptoms. Thus, even though one-half our population was symptomatic, the population was heavily skewed toward atypical chest pain symptoms and a relatively low likelihood of CAD, averaging <25% CAD likelihood.

Additionally, one-half of the patients were asymptomatic. Although all patients in this study were referred for MPS by their physicians, it should be noted that there are currently no class Ia indications for stress MPS in asymptomatic individuals (38). It is possible that some of the interrelationships noted in this study, such as the relative strength of chest pain symptoms to predict myocardial ischemia, would have been affected had we been able to incorporate more patients with typical angina into this study. Similarly, our ability to perform subanalyses, such as the impact of symptoms and gender effects, had limited statistical power owing to the relatively low frequency of MPS ischemia in our study. Accordingly, prospective studies that focus on the inter-relationship between MPS studies and calcium scores in populations containing more patients with typical angina and/or inducible myocardial ischemia would be useful for extending our findings.

Finally, as CAC matures as a testing modality in cardiology, it will be interesting to evaluate whether the perceived accuracy of this test is subject to patient referral bias, as has been observed for other noninvasive tests in cardiology (39).

Clinical implications. Three broad implications emanate from our results. First, they help to define the future indications for stress MPS referral after CAC imaging. Specifically, it appears that the referral of patients for MPS is generally not needed when the CAC score is <100 due to the very low likelihood of observing inducible myocardial ischemia in such patients. Conversely, when the CAC score exceeds 400, stress imaging would appear to be generally beneficial, because the frequency of inducible ischemia is substantial within this CAC range, even in asymptomatic patients.

Second, our results indicate that CAC scores in the range of 100 to 400 constitute a relatively large "gray zone" relative to the issue of who may require stress-test referral following CAC imaging. Pending confirmation, our results suggest that within this range of CAC scores, clinical factors such as symptoms, gender, coronary risk factors, and stress ECG results may serve to impact substantially on the observed frequency of MPS ischemia. Accordingly, future studies involving large number of patients with CAC scores in the range of 100 to 400 are needed to define the best combination of clinical predictors for predicting an ischemic MPS study in this CAC score range. In general, however, it appears from our data that within this range, any threshold for referral to MPS testing following CAC scanning should be *lower* among symptomatic patients or among those of male gender. Conversely, an asymptomatic presentation is likely to be associated with a higher recommended CAC threshold value before referral for stress testing becomes cost-effective after CAC scanning.

One potential approach to determining whether MPS would be of value in a given patient might be to combine the CAC score with all other relevant clinical and historical information into a Bayesian estimate of likelihood for angiographically significant CAD, as suggested by a recent study (39). However, more work is needed to validate this approach and compare it with other potential approaches for integrating the results of CAC scanning into clinical practice, such as the use of the Framingham risk score in asymptomatic patients.

Third, the wide range of CAC scores in our patients with normal MPS studies exposes an important limitation relevant to all forms of stress testing: they do not effectively screen for subclinical atherosclerosis. For instance, only 22% of our patients with a normal SPECT study had no evidence of CAC, 56% had a CAC score ≥100, and 31% had a CAC score ≥400. Further, even among those with CAC scores ≥1,000, 85% of asymptomatic and nearly 68% of symptomatic patients had a normal MPS study.

Along these lines, there are yet no available data to compare the relative short and long-term risk for cardiac events among patients with various combinations of MPS results and CAC scores, such as those presenting with the combination of very high CAC scores but normal MPS results. It is reasonable to hypothesize that such patients might be at low *short-term* risk but high *long-term* risk for cardiac events. If so, CAC could then be unmasking a subgroup of patients who would receive more aggressive anti-atherosclerotic intervention than would have been indicated based on the results of MPS testing alone. Accordingly, future studies incorporating the prognostic follow-up data from patients undergoing both studies would now be of interest, so as to determine which patients with normal stress imaging tests are best suited for undergoing *subsequent* CAC scanning.

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