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Original article

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The relationship between stress-induced myocardial ischemia and coronary artery atherosclerosis measured by hybrid SPECT/CT camera

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Running Title: CAC and MPI by hybrid SPECT/CT

ABSTRACT

Objective: The coronary artery calcium (CAC) score and myocardial perfusion imaging can now be detected simultaneously using a hybrid SPECT/CT camera. However, there has been little evaluation on the relationship between stress-induced ischemia and coronary artery calcification in a Japanese population. The aim of this study was to investigate the relationship between these parameters and to elucidate the diagnostic value of the CAC score as an adjunct to myocardial perfusion imaging (MPI) for the assessment of coronary artery disease (CAD) in an intermediate-risk population. Methods: We retrospectively analyzed 105 patients (63% men, mean age 71 years) with CAD or suspected CAD who underwent MPI using SPECT/CT. CAC scanning was performed by using a SPECT/CT camera. Results: There was a significant difference in the CAC score between patients with ischemia (n=42) and those without ischemia (n=63) (1353±1524 vs. 332±554, p<0.01). The frequency of ischemic MPI determined by summed difference score tended to be higher in patients with high CAC (CAC=0; 0.8±1.3 vs. CAC>1000; 3.0±2.0). Higher age is related roughly with higher CAC score with no statistical significance (r2=0.1) (<60 years old; 200±692, v.s. 80 years old <; 1258±1546, ns). The location of calcification was not related to the ischemic area. In a population with a predominately intermediate likelihood of CAD, a calcium score of zero has a possibility of excluding inducible ischemia on MPI. In part, ischemic MPI is associated with a high likelihood of subclinical atherosclerosis as detected by CAC. Conclusion: Hybrid SPECT/CT might be useful for diagnostic assessment and coronary artery with known or suspected CAD.

Introduction

Risk stratification is essential in the management of coronary artery disease. Myocardial perfusion imaging (MPI) using ECG-gated SPECT can offer incremental important prognostic information on the subjects [1-3]. Nuclear cardiology techniques are uniquely advanced to address the determinants of prognosis by measuring stress-induced ischemia or function. These measurements include the extent of infracted myocardium and the amount of jeopardized myocardium [4].

Recent advances in hardware using hybrid SPECT/CT have allowed the combined assessment of perfusion and coronary atherosclerosis [5]. Coronary artery calcification is a highly sensitive marker of underlying coronary atherosclerotic disease [6-8]. Calcification is a regulated process prompted by inflammation in the coronary artery. The amount of coronary artery calcium is considered to reflect the patient’s coronary atherosclerotic burden and correlates closely with the likelihood of future cardiovascular events [9]. A hybrid SPECT/CT system may provide this kind of prognostic information without any extra-cost. A combined approach of calcium scoring and myocardial perfusion may assist in identifying a large number of patients who might benefit from aggressive medical management.

The objectives of this study were to determine the relationship between myocardial perfusion abnormalities and coronary artery atherosclerosis by using a SPECT/CT hybrid camera.

Materials and methods

Subjects

We reviewed 105 patients (mean age 71 ± 12.4 years, 63% male) who completed combined stress perfusion imaging and CAC scoring on a hybrid SPECT/CT scanner

[10]. Patients were referred for stress MPI on clinical grounds, and CAC scoring was performed as a routine component of each study.

Clinical and Historical Data

Clinical histories elicited at the time of examination ascertained the presence or absence of various cardiac symptoms and risk factors, including diabetes mellitus, hypertension, hyperlipidemia and chronic kidney disease. Baseline measurements were obtained for the following: high density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, blood urea nitrogen and creatinine.

Stress myocardial perfusion Imaging

All 105 patients underwent stress ^{99m}Tc-sestamibi (MIBI) imaging or 99mTc-tetrofosmin. The protocol of stress scan was performed according to Japanese Circulation Society guideline [11]. In 15 patients, exercise myocardial perfusion imaging was performed with one-day stress-rest sequence protocol as symptom-limited multi-step exercise using a bicycle ergometer [12]. ^{99m}Tc-sestamibi (MIBI) or ^{99m}Tc-tetrofosmin (300-370MBq) was administered when submaximal heart rate, chest pain, ST-segment depression, or leg fatigue occurred. A standard 12-lead ECG was monitored continuously during infusion and was printed every minute. An ischemic response was defined as >1-mm, flat or down-sloping, ST-segment depression or >1.5-mm, up-sloping, ST-segment depression in >2 contiguous lead at 80 ms from the J point. Then, exercise was continued for 1 minute at the same level as before [13]. Pharmacological stress by adenosine was performed in the remaining 90 patients. Patients were asked to discontinue β-blockers for 48 h, and caffeine for 24 h prior to the study. Adenosine was administered intravenously at a standard infusion rate of 120 μg/kg/min for 6 minutes. A tracer (^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin) was injected at 3 minutes during the adenosine infusion. After image acquisition, the patients were given the tracer (740 MBq) while at rest. More than thirty minutes later, ECG-gated image acquisition was started. In both kinds of protocol, ECG-gated SPECT images were acquired with a 64 x 64 matrix, 6-degree step and 360-degree rotation using a dual-head detector camera (Symbia T6, Siemens Co. Tokyo, Japan) without x-ray-based attenuation correction. The division of the R-R interval was 16.

Image interpretation

Myocardial perfusion defects were scored semi-quantitatively by QPS (quantitative scoring SPECT) software and confirmed by two experienced nuclear cardiologists (S.M., K.N.). A 17-segment model of the left ventricle was used with a 5-point scale (0 = normal uptake, 1 = mild hypoperfusion, 2 = moderate hypoperfusion, 3 = severe hypoperfusion and 4 = no uptake) [10]. Summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of 17 segments on the stress and the rest images, respectively. Summed difference score (SDS) was derived as the difference between the stress and rest scores. SSS<3 was considered normal; 3-7, mildly abnormal; 8-11, moderately abnormal; >12, severely abnormal. Similarly, for the degree of reversibility, SDS <2 was considered non-ischemic. The interpretations were defined as follows: (1) normal (homogenous uptake), (2) ischemia (perfusion defects on post-stress images that completely or partially corrected on rest images, SDS>1), (3) infarct (fixed defect was defined as a region with a score at stress of>1 without an improvement at rest). Resting ECG-gated SPECT was quantitatively analyzed with gated QGS/QPS software (Cedars QGS/QPS; Cedars-Sinai Medical Center, Los Angeles, CA) to calculate volumes and ejection fraction.

CAC CT Acquisition and Reconstruction

After myocardial perfusion imaging, all patients underwent a CT scan for CAC scoring using a SPECT-CT scanner (Symbia T6, Siemens, German). Breath-holding instructions were given to minimize misregistration. This gated CT scan (120 kV; 50 mA) was acquired and reconstructed with filtered back-projection and a standard convolution kernel to 2.5-mm slices with a 512 x 512 matrix and a fixed 25-cm field of view.

CAC Scoring

Scoring was performed by an experienced independent observer who was blinded to the patients' clinical history, outcomes, and MPI scan results. Agatston scores were computed with commercially available software (TruePoint, Siemens) [14]. Artery-specific scores were summed across lesions identified in the left main, left anterior descending, left circumflex, and right coronary arteries to provide a total CAC score for each patient. The CAC was identified as a dense area at the location of a coronary artery exceeding the threshold of 130 HU. An overall Agatston score was recorded for each coronary artery and per patient. Standard categorization of Agatston scoring was applied: less than 10, minimal; 11-100, mild; 101 to 400, moderate; 401 to 1000, severe; greater than 1,000, extensive.

CT Coronary Angiography

CT coronary angiography was performed, when it was needed, by using a 64-detector CT scanner (light Speed VCT; GE Healthcare) [10]. A semi-quantitative visual assessment of image quality score was performed. The following criteria was used: for score 0 (good quality), clinical imaging interpretation was reliable and easy to evaluate coronary stenosis. The interpretation, which was still suitable but more difficult for determination of the degree of stenosis because of calcification, was defined as a score of 1 (fair quality). When there was no reliable clinical image interpretation in terms of visibility of the vascular lumen due to any reason including calcification, the image was considered as a score 2 (poor quality).

Statistical Analyses

Statistical analysis was performed using the computer-based program Statistical Discovery Software JMP (version 5.0.1. SAS institute, Cary, NC). A student’s t test was used for comparison of means. Descriptive data are presented as mean ± SD or simple proportions as appropriate. P-values for categorical variables were calculated by one-way ANOVA. A p-value of <0.05 was considered statistically significant.

Results

Relevant clinical characteristics of the study population are listed in Table 1. We examined baseline coronary artery calcium scores. The prevalence of CAC scores was as follows. No CAC was present in 15 patients (14%). Ninety patients (86%) had evidence of CAC. Based on Agatston scoring, the amount of calcium was minimal in 6 (6%) patients, and mild in 17 (16%) patients, moderate in 26 (25%) patients, and severe in 41 (39%). Of 41 patients with an Agatston score greater than 401, 25 of them had an extensive CAC score greater than 1,000. A representative case with a high CAC score is shown in Figure 1. A 72-year-old man with a 3150 calcium score represents inferolateral ischemia of left ventricle on the stress imaging. CAC scores in the left descending coronary artery, left circumflex, right coronary artery, and left main trunk are separately listed as 2037, 670, 442, and 1, respectively. The possible indication of CT angiography was determined when a high calcium score makes it difficult to detect the degree of stenosis by using CT

CAC tends to be higher with advancing age (200 ± 629 (age < 60); 596 ± 1069 (60 < age < 70); 936 ± 1247 (70 < age); $p < 0.05$, Figure 2). A higher age tends to be related with higher CAC score with no statistical significance. There was no statistical significance in the CAC score between male and female (660 ± 1060 vs. 876 ± 1314, ns).

Relationship between CAC score and ischemia

Overall, the frequency of ischemia increased with the CAC score. The calcium score weakly correlated with the severity of ischemia expressed by SDS (r^2=0.066, ns). We also observed a significantly higher frequency of abnormal scans among patients with CAC≥of 400 (48.5%, p<0.001). Perfusion abnormalities expressed by SSS were significantly higher in patients with a CAC > 1000 in comparison to subjects without calcification (p=0.02). Subjects with a severe CAC score had a high frequency of ischemia compared with subjects without calcification (SDS=2.5± 2.0 vs. 0.8±1.3, p=0.006). The patients with ischemia had much higher calcium scores on average than patients without ischemia (P<0.001) as shown in Figure 3.

There was a significant difference in the CAC score between patients with ischemia (n=42) and those without ischemia (n=63) (1353 ± 1524 vs. 332 ± 554, p<0.01). The frequency of ischemic MPI determined by summed difference score tended to be higher in patients with high CAC (CAC=0; 1.2 ± 1.9 vs. CAC > 1000; 5.2

± 6.3) (Figure 4). The location of calcification was not related with the ischemic area. Myocardial perfusion abnormalities expressed by SSS tends to become higher as coronary calcification increases (Figure 4). In a population with predominately intermediate likelihood of CAD, a calcium score of zero was able to exclude inducible ischemia on MPI in 13 out of 15 subjects. The overall sensitivity for the CAC score of 0 to predict the absence of perfusion abnormality was 87 %.

CAC score in normal MPI

There are 52 subjects (70.3 ± 13.6 years old) with normal stress MPI who participated in this study. The CAC score was 347 ± 576. The distribution of CAC in patients with normal perfusion imaging is shown in table 2. Among 14 subjects with normal MPI and high CAC (≥400), there was one patients with transient ischemic dilatation. There were no significant difference between stress functional parameters and rest parameters such as EDV, ESV and EF (NS).

Status of CT angiography

CTA was conducted in 40 cases. CTA image quality was good in 23 (58%) of the cases, fair in 11 (28%), and poor in 6 (15%). The CAC score in patients with good images was 347 ± 560, the fair image was 1312 ± 1298, and the poor image was 2251 ± 1891. There was a significant difference in the CAC score between image qualities ($p<0.001$).

Discussion

Our study indicates that CAC scores increase with advancing age, reflecting the natural progression of atherosclerosis in accordance with that of previous studies [1, 15]. The present study showed by using SPECT/CT hybrid system the relationship between CAC and the frequency of myocardial perfusion abnormalities in patients with known or suspected CAD, describing the interrelation of CAC and myocardial perfusion abnormalities. This suggests that the degree of coronary atherosclerotic burden obtained by SPECT/CT can be used to elucidate a potential indicator of cardiovascular risk for its complementary diagnosis with MPI [7].

Relationship between CAC and Ischemia

Determination of coronary calcium is supported by large population studies reporting high major adverse cardiac event rates in patients with a high CAC score [16]. CAC scores are generally predictive of a higher likelihood of ischemia on MPI [8]. Grouping the subjects by calcium score clearly demonstrated a trend toward ischemia and infarction on MPI in patients with increasing CAC scores, especially among patients with a CAC≥of 1000. The subjects without coronary calcification have reportedly very low prevalence of myocardial perfusion abnormalities when it is used as screening of CAD [15]. Previous studies have assessed the relationship between CAC and myocardial ischemia as measured by SPECT, and these primarily used a screening population [1]. A negative calcium scan (CAC=0) affords a high negative predictive value when it is used to evaluate the population for screening CAD [15]. However, when it is used to evaluate the populations of suspected CAD, the subjects with CAC scores of <10 were less relevant with a normal MPI. In fact, the absence of CAC did not confer normal and abnormal MPI, which limited the predictive value of CAC scoring in patients with known or suspected CAD. Our study showed that subjects with inducible myocardial ischemia had a higher CAC score than those without ischemia. This study is concordant with previous studies in the USA [17], although the prevalence of subclinical atherosclerosis in Japanese men was strikingly lower than those of American men. A proportional relationship was demonstrated between the CAC score and the frequency of adverse cardiac events [8]. A further prognostic study is absolutely needed to establish more precise clinical value in risk stratification.

CAC in patients with normal SPECT

In a previous study in a large-scale clinical trial, a clear association has been demonstrated between the extent of perfusion abnormalities and risk of coronary events [3]. Also, another previous study showed that normal stress myocardial perfusion imaging is associated with low risk of cardiovascular risk with an annual event rate of 0.6-0.9% [2, 11, 18]. However, the wide range of CAC scores in patients with normal MPI suggests that stress perfusion imaging is limited in its ability to detect subclinical atherosclerosis. There is no evidence to compare the relative short and long-term risk for cardiac events among patients with both myocardial perfusion imaging and calcium evaluation. A previous study showed that the cardiac event rate in elderly and diabetic patients with normal MPI was relatively higher than that in younger and non-diabetic patients [11]. Our study also suggests that each subject with normal SPECT may differ in the stage of atherosclerosis and have a different atherosclerotic burden in the coronary artery. Then what about the patients with high CAC and normal MPI? We assume such patients might have low risk in the short-term but high risk in the long term for cardiovascular events, since patients with high CAC have been reportedly regarded as high risk patients [17]. Previous studies suggest patients without ischemia on MPI exhibit a stepwise increase in their risk of cardiac events with increasing CAC scores, indicating there might exist a warranty period for normal SPECT imaging [18, 19]. Even if the MPI is normal, the addition of the CAC score may improve the detection of CAD, particularly severe multivessel CAD. The documentation of CAC as a marker of coronary atherosclerosis can be used to target patients requiring more intensive management of coronary risk factors.

We can assume that subjects with a low baseline CAC score and ischemia, when high sensitive C reactive protein is elevated, might have a kind of prevailing soft lipid-rich plaque with more active inflammatory processes; progression occurring in a still inflamed and unstable plaque might have reduced survival. In contrast, a high baseline CAC score was likely a sign of stable plaque with less active or absent inflammatory lesions, and the progression in this plaque might have occurred due to factors other than inflammation with minor impact on survival.

SPECT/CT hybrid system

A hybrid SPECT/CT system has been introduced recently in clinical settings and been available in many countries. The CAC score can be used to estimate the total magnitude of atherosclerotic burden. MPI has been an essential component in physicians' diagnostic and prognostic assessment of patients. Combined SPECT/CT acquisition in a one stop examination is more acceptable, and physicians can obtain perfusion and calcification information without any extra-cost [5]. CAC score data provide information on the rate of absolute and relative progression of calcification [19]. The value of sequential calcium scoring for documentation of the efficacy of statins in reducing the progression of coronary atherosclerosis was recognized [20]. The combination of CAC and MPI can be effectively used for monitoring aggressive risk factor modification and optimal medical therapy [20]. The integration of myocardial perfusion imaging and the CAC score is an interesting strategy for the diagnostic work-up of patients [21]. A recent clinical trial revealed that CAC scanning can improve cardiac management without incurring increase in downstream medical costs. Hybrid imaging can provide an accurate special alignment and is feasible for attenuation correction. The single session hybrid imaging is likely to be preferred since it results in obvious benefits for the patients. Since high CAC makes it difficult to evaluate coronary artery stenosis, SPECT/CT might be useful for the decision making process with regard to performing CT angiography. However, precise clinical implication for the prediction of risk of patients by a hybrid imaging system remains to be elucidated by further investigation. A further prognostic study is absolutely needed to establish more precise clinical value in risk stratification.

Conclusions

Hybrid SPECT/CT might be useful to make diagnostic assessment in one session in patients with known or suspected CAD. The integration of myocardial perfusion imaging and the CAC score may offer additional benefit for the diagnostic work-up of patients.

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Tables and figures

Table 1

Characteristics of patients

Age (years old)	71±12.4
Sex (male/female)	66/39
Risk factors	
Hypertension	67 (64%)
Diabetes mellitus	60 (57%)
Dyslipidemia	25 (24%)
Chronic kidney disease	15 (14%)
Laboratory data	mean ± SD
BUN	20.7 ± 16.2
Cre	1.2 ± 1.5
LDL-C	114.0 ± 32.7
HDL-C	49.5 ± 15.7
TG	120.0 ± 61.2

BUN, blood urea nitrogen; Cre, creatinine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerie.

Table 2

Distribution of CAC in patients with normal myocardial perfusion

CAC	n	
0	11	0
0-10	6	3.7±3.6
10-100	12	45.9±24.6
100-400	9	210.6±88.1
400-1000	8	723.7±212.8
1000-	6	1637.3±656

CAC, coronary artery calcium score

Figure 1.

A case of a 71-year-old male outpatient with high calcium score and severe stenosis on the middle portion of the left circumflex coronary artery, Calcium was observed in the left descending coronary and left circumflex coronary (A). His stress myocardial perfusion imaging showed inferolateral ischemia on automatic score (B) and on SPECT imaging (C).

SA, short axis; VLA, vertical long axis; HLA, horizontal long axis.

Figure 2. A correlation between coronary calcification and age.

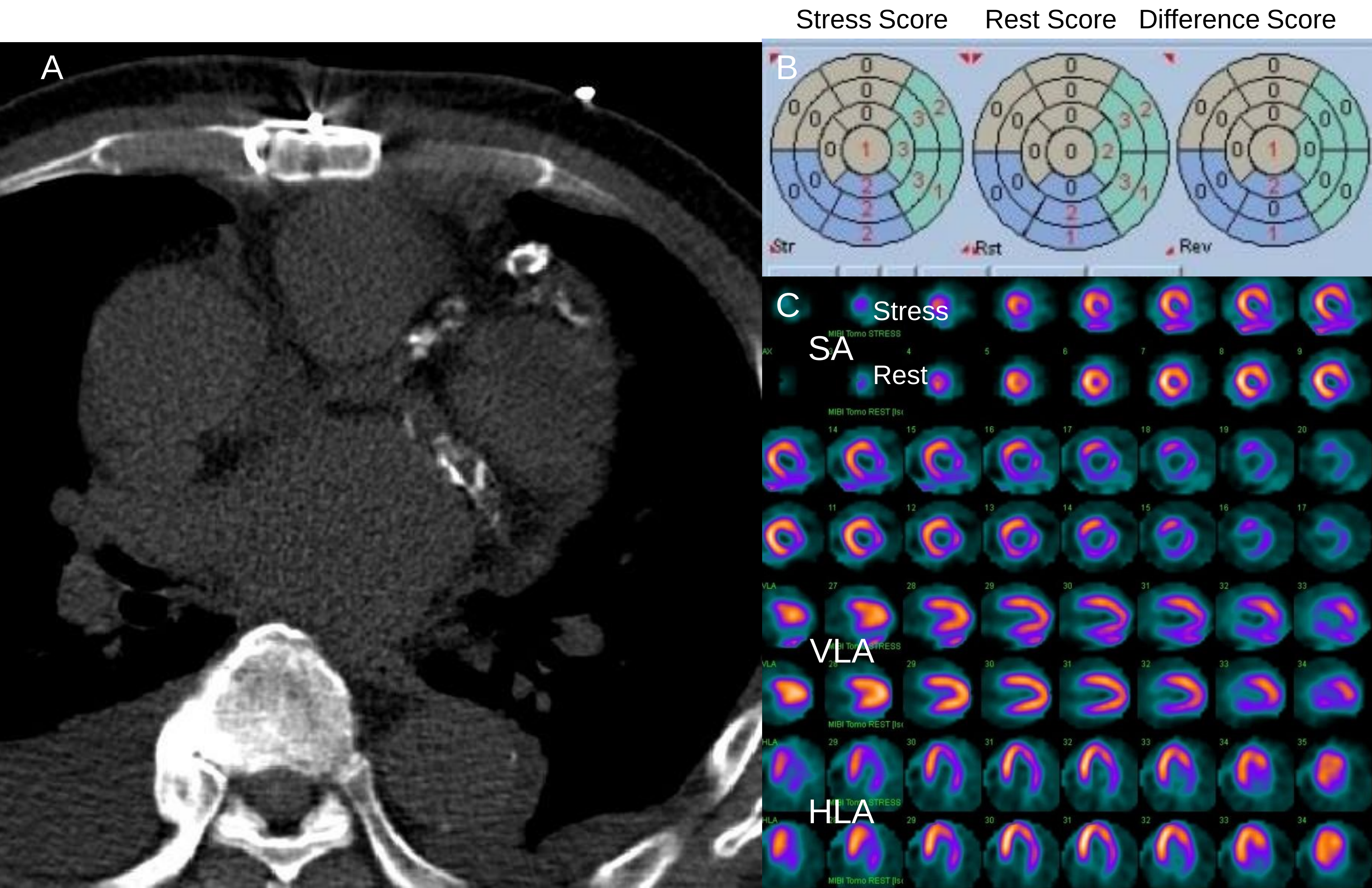
Calcium score tends to be higher with advancing age.

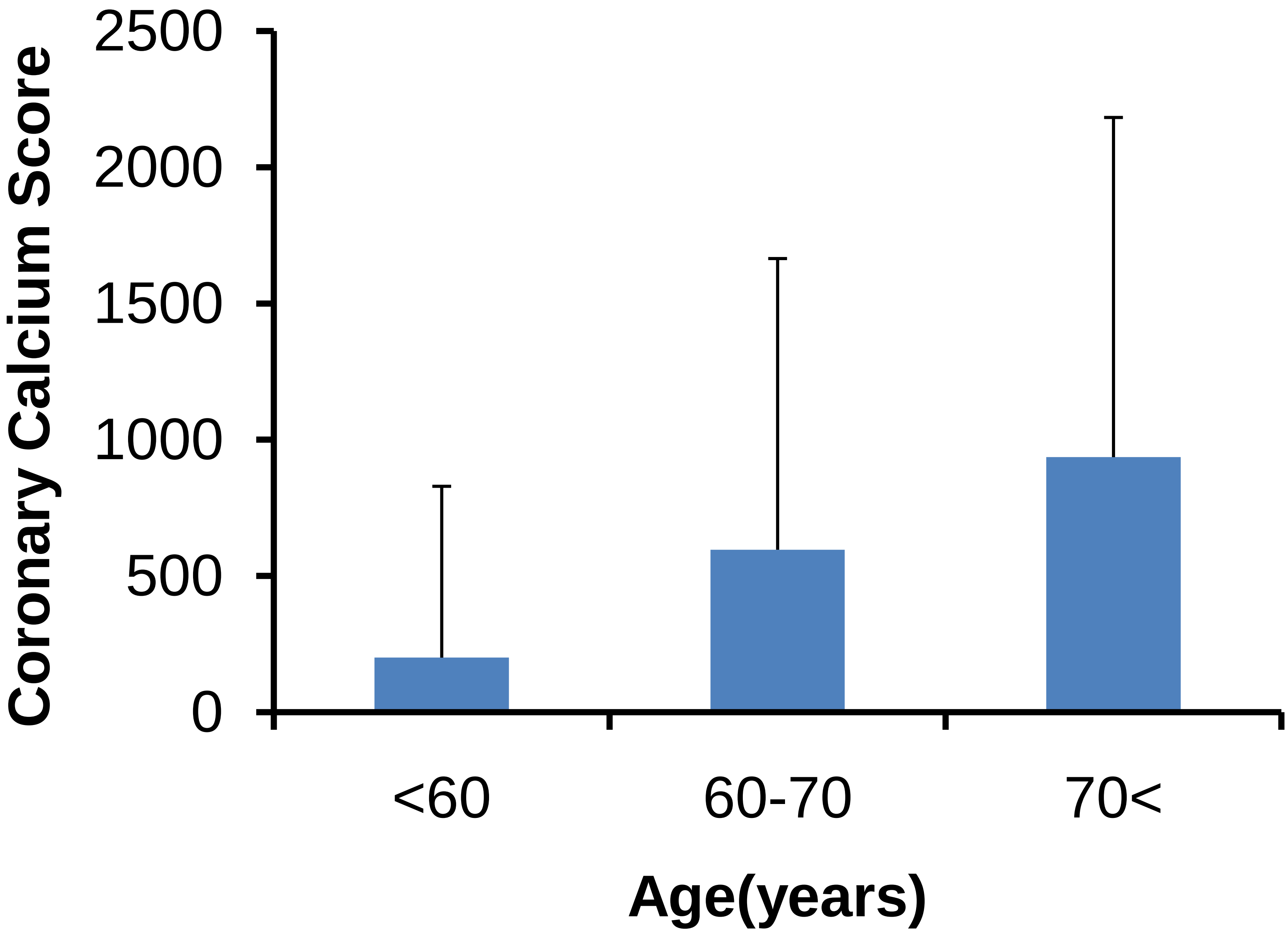
Figure 3. A correlation analysis between coronary calcification and ischemia. Subjects with ischemia had a much higher calcium score than those without ischemia.

Figure 4. Coronary artery calcification score and MPI scores.

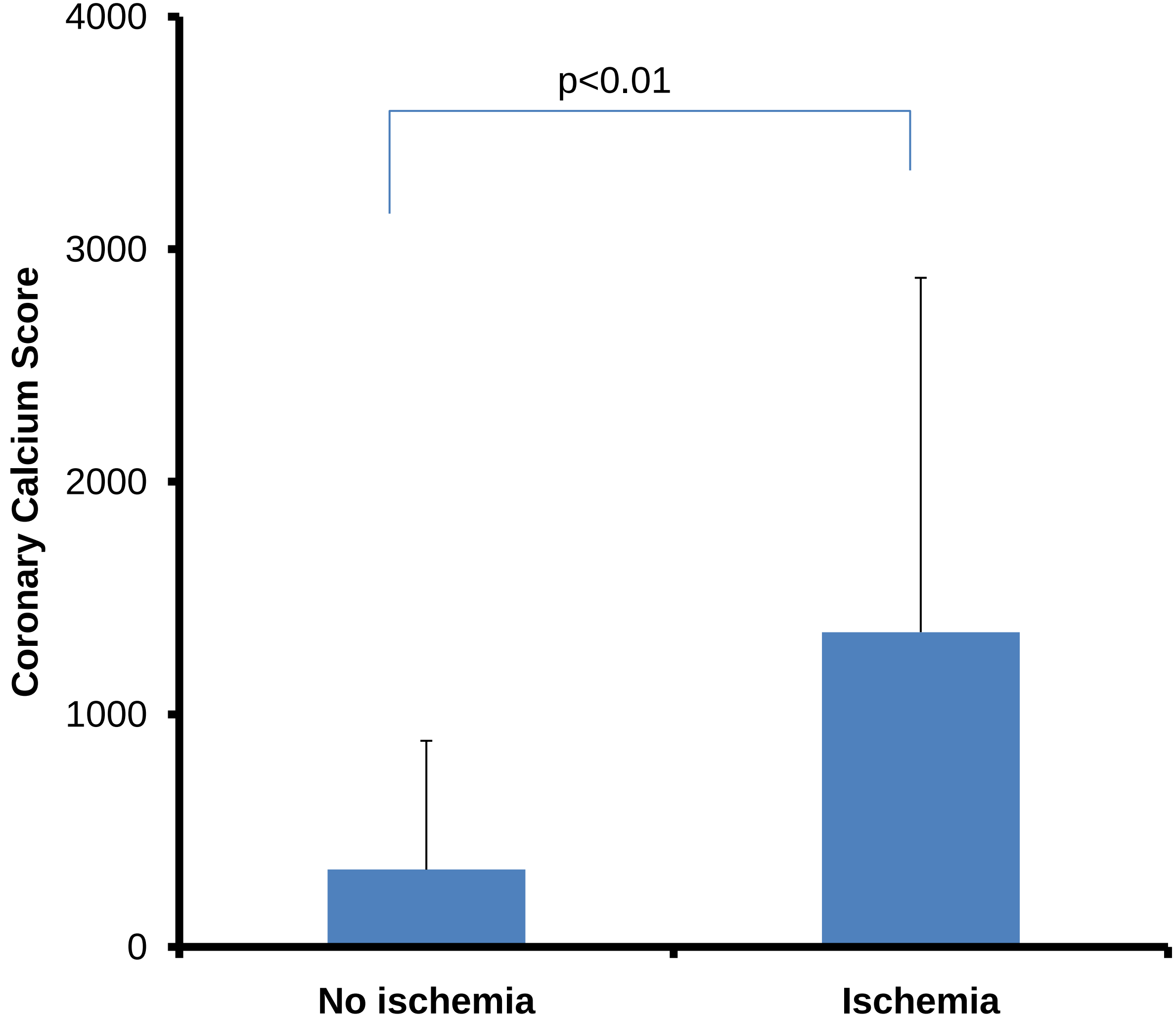
The frequency of ischemic MPI determined by SDS tends to be higher in patients with high coronary artery calcification. SSS tends to become higher as coronary calcification increases.

MPI, myocardial perfusion imaging; SSS, summed stress score; SDS, summed difference score.


Stress Score
Rest Score
Difference Score
A
B
Str
Rst
Rev
C
Stress
SA
Rest
MIBI Tomo STRESS
MIBI Tomo REST
VLA
HLA



Coronary Calcium Score
2500
2000
1500
1000
500
0
<60
60-70
70<
Age(years)



Coronary Calcium Score
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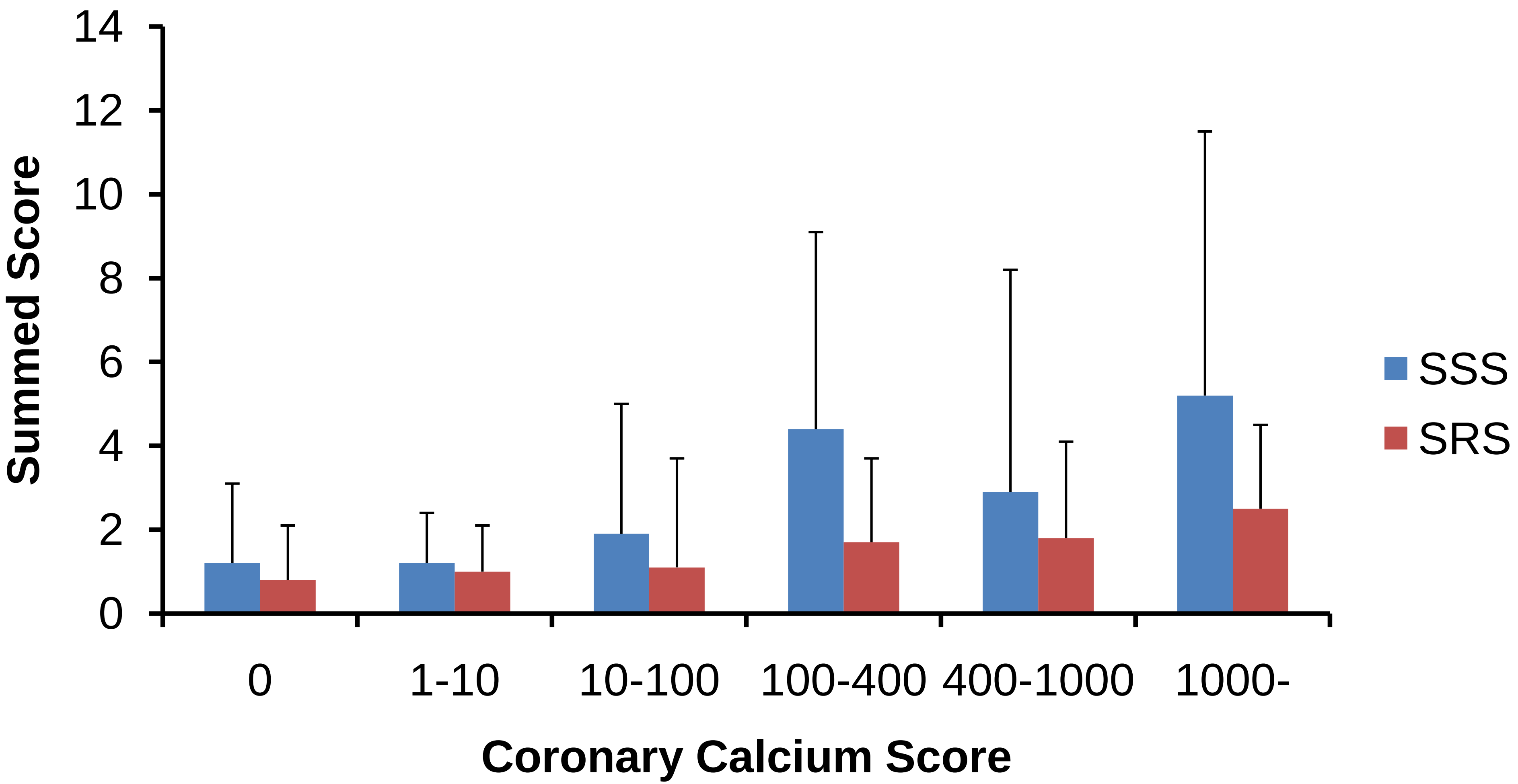
3000
2000
1000
0
p<0.01
No ischemia
Ischemia



14
12
10
8
6
4
2
0
Summed Score
0
1-10
10-100
100-400
400-1000
1000-
Coronary Calcium Score
SSS
SRS