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Quantitative Relation between Coronary Calcium Content and Coronary Flow Reserve as Assessed by Integrated PET-CT Imaging

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Abstract

Background—Coronary artery calcium (CAC) is a marker of atherosclerosis. Whether epicardial calcium reflects more widespread atherosclerosis affecting coronary vascular function is unknown.

Methods—We evaluated 136 consecutive patients without known coronary disease (age 62 ± 12 years, 68 % females) undergoing vasodilator stress ^{82}Rb PET and CAC scoring based on clinical grounds. Patients with normal myocardial perfusion on standard semi-quantitative analysis were included. The Agatston CAC score, rest and stress myocardial blood flow (MBF), coronary flow reserve (CFR) and coronary vascular resistance (CVR) were quantified and analyzed on a per patient and per vascular territory basis.

Results—Global and regional CAC scores showed modest but significant correlation with hyperemic MBF ($r = -0.31$ and $r = -0.26$, $p \leq 0.0002$, respectively), CFR ($r = -0.28$ and $r = -0.2$, $p \leq 0.001$, respectively), and CVR during peak hyperemia ($r = 0.32$ and $r = 0.26$, $p \leq 0.0002$, respectively). There was a modest stepwise decline of mean CFR with increasing CAC score on per patient analysis (1.8 ± 0.5 vs 1.7 ± 0.5 vs 1.5 ± 0.4 , $p = 0.048$ with total CAC = 0, 1–400 and >400 respectively) and per vessel analysis (1.8 ± 0.6 vs 1.6 ± 0.4 vs 1.5 ± 0.5 vs 1.5 ± 0.5 , $p = 0.004$ with vessel CAC score = 0, 1–100, 101–400 and >400 respectively). In multivariable modeling only body mass index ($p = 0.005$), CAC score ($p = 0.04$) and hypertension ($p = 0.05$) remained predictive.

Conclusions—In patients without overt CAD, there is a modest but statistically significant inverse relationship between CAC content and coronary vasodilator function, which persists after adjusting for the effect of coronary risk factors.

Keywords

coronary calcifications; coronary flow reserve; coronary atherosclerosis; positron emission tomography

Background

Coronary artery calcium (CAC) is absent in normal coronary arteries, and its presence is indicative of atherosclerosis. Studies using CT to detect and measure CAC have shown a good correlation between calcium content and overall coronary atherosclerotic burden(1,2). The observation that coronary calcium content is lower in patients with acute coronary syndromes compared to those with stable CAD has been interpreted as a sign of clinical stability and that calcification likely represents a healing response. (3,4) However, data from several large prospective studies demonstrating a stepwise increase in coronary risk with increasing calcium scores challenge the notion that calcified coronary disease represents a scenario of clinical stability. (3-9) Indeed, conventional risk factors do not fully account for the excess coronary risk observed with increasing calcium scores. This suggests that other mechanisms may contribute to the association between coronary calcification and the increased risk of CAD. Since CAC is likely to reflect more widespread atherosclerosis, we reasoned that one such mechanism might involve the potential adverse effect of widespread atherosclerosis on vascular function, thereby increasing the potential for coronary vasoconstriction and thrombosis.(10)

Our objective was to determine the relationship between the magnitude of coronary calcification assessed by CT and coronary vasodilator function as assessed by quantitative PET imaging.

Methods

Patient Population

We reviewed 200 consecutive patients who completed combined rest-stress Rubidium-82 PET perfusion imaging and CAC scoring on a hybrid PET-CT scanner from November 2005 to August 2007. Patients were referred for cardiac PET-CT imaging for investigation of chest pain or non-classic symptoms with multiple CAD risk factors, and CAC scoring was performed as a routine component of each study. Patients with known CAD (defined by a history of prior myocardial infarction and/or evidence of pathologic Q waves on resting ECG or prior revascularization) were excluded, as were those with cardiomyopathy (defined as LVEF<40%), and/or conditions that would preclude reliable gated CT imaging for CAC assessment (arrhythmia, patient motion, presence of cardiac pacemaker or defibrillator leads). In order to avoid the potential confounding effect of epicardial stenosis on myocardial blood flow, only consecutive patients with normal PET scans on standard semiquantitative analysis were selected for this analysis (n=136). The study was approved by the Partners Human Research Committee.

Clinical and historical data

Clinical histories elicited at the time of exam ascertained the presence or absence of various cardiac symptoms and risk factors, including chest pain, dyspnea, medications, family history of premature CAD, diabetes mellitus, hypertension, hyperlipidemia, and current or past cigarette smoking. Height and weight were recorded, and body mass index (BMI) was calculated. Pretest likelihood of CAD was assigned according to age, sex, symptoms and other risk factors.(11)

Hybrid PET/CT imaging

All patients were studied using a whole body PET-CT scanner (Discovery STE LightSpeed 64, GE Healthcare, Milwaukee, WI) following an overnight fast and 24-hour cessation of all caffeine or methylxanthine containing substances.

Assessment of Myocardial Blood Flow—Myocardial blood flow (MBF) was measured at rest and during peak hyperemia using ^{82}Rb as a flow tracer. Following a scout CT scan (120 kVp, 10 mA) used for proper patient positioning, a CT transmission scan was acquired (140 kVp, 10 mA) for subsequent correction of photon attenuation. Beginning with the i.v. bolus administration of ^{82}Rb (1,480–2,220 MBq), serial images were acquired for 7 minutes as previously described (12). Then, intravenous dipyridamole (0.142 mg/kg/min for 4 minutes, n=129 patients) or adenosine (0.14 mg/kg/min for 6 minutes, n=7 patients) was infused. At peak hyperemia, a second dose of ^{82}Rb (1,480–2,220 MBq) was injected and images were recorded using the same acquisition sequence. A second CT transmission scan was acquired (140 kVp, 10 mA) after vasodilator stress for attenuation correction of the stress emission data. The heart rate, systemic blood pressure, and 12-lead electrocardiogram were recorded at baseline and every minute during and after the infusion of the vasodilator. The rate pressure product was calculated as heart rate times systolic blood pressure at rest and during peak hyperemia respectively.

Assessment of Coronary Artery Calcification—After myocardial perfusion imaging, the patients underwent a CT scan for CAC scoring on the integrated 64-slice MDCT scanner (collimation $64 \times 0.625\text{mm}$, pitch 0.625:1, gantry rotation time 350 ms) using prospective gating at 80% of R-R interval. Breath-holding instructions were given to minimize misregistration. This gated CT scan (120 kV; 400 mA) was acquired and reconstructed using filtered back projection and a standard convolution kernel to 2.5 mm thick slices with a 512×512 matrix and a fixed 25-cm field of view.

Data Analysis

Semi-quantitative assessment of myocardial perfusion—Attenuation-corrected perfusion images were processed for viewing in the standard cardiac axis projections. Semi quantitative visual interpretation of the rest and stress perfusion images was performed using a 17-segment heart model.¹⁶ Segments were scored using the standard 5-point score (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = absence of detectable tracer uptake). Individual segmental scores were added together to obtain the summed stress score (SSS) and summed rest score (SRS). The difference between SSS and SRS was defined as the summed difference score. An absolute SSS >1 was considered abnormal. Only patients with normal perfusion on semi-quantitative PET interpretation were included in this analysis.

Quantitative assessment of myocardial blood flow—The transaxial, attenuation corrected perfusion images were reoriented into standard oblique planes (short axis, vertical and horizontal long axis of the heart). From those, the blood pool and myocardial time activity curves were constructed using Generalized Factor Analysis of the Dynamic Sequences software developed and validated at our institution. Regional MBF was calculated by fitting the ^{82}Rb time-activity curves with a two-compartment tracer kinetic model and modeled extraction fraction (12–14). Parametric polar maps were then constructed to calculate rest and peak stress regional MBF in each of the three major coronary artery territories, i.e. left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) territories based on the standard 17-segment heart model (15). The CFR was defined as the ratio between hyperemic and resting MBF. Coronary vascular resistance (CVR) was calculated by dividing the mean arterial pressure by MBF.

Coronary artery calcium scoring—CAC content was quantified using the method described by Agatston (16) and a semiautomated commercially available software (SmartScore, GE Healthcare). Coronary artery specific scores were calculated in the LAD (included calcium present in the left main coronary artery), LCX, and RCA arteries and then

summed to provide a total CAC score for each patient. The CAC score percentile ranks were determined for each individual patient based on gender and age specific CAC distributions as previously published in a large database of patients.(17)

Statistical analysis

Continuous variables are presented as mean $\pm$ SD and ordinal variables are summarized by count and percentages. Differences in hemodynamic characteristics, MBF, CFR and CVR from rest to stress were assessed using paired t-test. Spearman correlation coefficients were used to describe the relationship between CAC score and corresponding MBF, CFR or CVR on per patient and per vessel basis respectively. Differences in MBF, CFR and CVR between groups stratified by CAC score were investigated using one-way ANOVA with Bonferroni correction for multiple pairwise comparisons. The determinants of CFR were assessed by univariable and multivariable linear logistic regression analysis. A p value less than 0.05 was used to define statistical significance. We used SAS statistical software for all analyses (version 9.1.3, SAS Institute Inc. Cary, North Carolina).

Results

Study patients

The baseline characteristics of the study patients are shown in Table 1. In general, coronary risk factors were prevalent and patients had an intermediate likelihood of CAD. The CAC score ranged from 0 to 6316 (mean CAC score 249 ± 528). There were 44 patients (32%) with CAC score of 0, 66 patients (49%) with CAC score 1-400 and 26 patients (19%) with CAC score >400.

Systemic hemodynamics

With the infusion of dipyridamole, the heart rate and rate-pressure product increased, whereas the systolic, diastolic and mean arterial blood pressure decreased significantly (Table 2).

Per patient analysis

Myocardial blood flow and coronary vascular resistance—Baseline and peak myocardial blood flow was regionally homogeneous and similar between the three coronary territories. During hyperemia, myocardial blood flow increased and coronary vascular resistance decreased significantly compared to baseline (Table 3).

Relationship between coronary artery calcium and vasodilator function—In the 136 patients, total CAC scores were inversely correlated with peak MBF ($r = -0.31$, $p=0.0002$), estimates of CFR ($r = -0.28$, $p=0.001$) and peak CVR ($r = 0.32$, $p=0.0002$). There was no correlation between CAC scores and baseline MBF ($r = -0.14$, $p=0.1$). Stratification of patients into 3 groups based on their CAC scores (0, 1-400, >400) resulted in stepwise reductions in mean peak MBF (1.9 ± 0.6 vs 1.7 ± 0.6 vs 1.4 ± 0.5 mL/min/g, respectively, $p=0.009$), mean CFR (1.8 ± 0.5 vs 1.7 ± 0.5 vs 1.5 ± 0.4 , respectively, $p=0.048$), and stepwise increases in mean peak CVR (53 ± 20 vs 60 ± 22 vs 72 ± 21 mmHg/mL/min/g, respectively, $p=0.003$) with increasing levels of CAC content. (Figure 1) No significant difference in mean baseline MBF was observed between the 3 CAC groups ($p=0.1$).

However, stratification of patients based on their gender and age specific percentiles of CAC (<25th, 25-75th, >75th percentiles groups) (17) resulted in weaker and non-significant correlations between CAC content and myocardial blood flow. There was a non-significant stepwise decline in peak MBF (1.8 ± 0.7 vs 1.7 ± 0.6 vs 1.5 ± 0.6 mL/min/g, respectively,

$p=0.08$), CFR (1.8 ± 0.6 vs 1.7 ± 0.5 vs 1.5 ± 0.4 , respectively, $p=0.05$), and a stepwise increase in mean peak CVR (56 ± 21 vs 58 ± 21 vs 67 ± 23 mmHg/ml/min/g, respectively, $p=0.06$). No significant difference in resting MBF was observed between the CAC percentile groups.

Predictors of coronary flow reserve—In univariable analysis, the predictors of flow reserve included hypertension ($p=0.01$), CAC score ($p=0.01$), body mass index ($p=0.01$) and diabetes ($p=0.02$). In multivariable modeling including factors that had been associated with impaired CFR (age, gender, history of hypertension, diabetes, dyslipidemia, smoking and obesity- represented by body mass index), only the body mass index ($p=0.008$) and history of hypertension ($p=0.03$) were independent predictors of CFR (model R-square = 0.15). When CAC score was added into the model, it was also predictive of CFR with improvement of the overall model ($p=0.04$, model R-square = 0.18). (Table 4)

Per vessel analysis

Relationship between coronary artery calcium and vasodilator function—In the 136 patients, there were total of 408 vascular territories analyzed. Per-vessel CAC scores correlated modestly with peak MBF ($r = -0.26$, $p<0.0001$), CFR ($r = -0.2$, $p<0.0001$), and peak CVR ($r = 0.26$, $p<0.0001$).

Stratification into groups of per-vessel CAC scores (0, 1-100, 101-400 and >400) resulted in stepwise reductions in mean peak MBF (1.8 ± 0.7 vs 1.6 ± 0.6 vs 1.5 ± 0.5 vs 1.4 ± 0.5 mL/min/g, respectively, $p<0.0001$), mean CFR (1.8 ± 0.6 vs 1.6 ± 0.4 vs 1.5 ± 0.5 vs 1.5 ± 0.5 , respectively, $p=0.004$) and stepwise increase in mean peak CVR (55 ± 21 vs 64 ± 24 vs 65 ± 21 vs 75 ± 24 mmHg/ml/min/g, respectively, $p<0.0001$) with increasing levels of CAC. (Figure 2)

Discussion

Coronary artery calcification on CT scanning has been assumed to be associated with clinical stability and to represent a healing response to atherosclerotic vascular complications (3,4,18). However, the observation of excess cardiovascular risk beyond that accounted for by traditional risk factors in the setting of increased coronary calcification has challenged these assumptions (4-9). Since CAC is likely to reflect more widespread atherosclerosis, we hypothesized that one potential mechanistic link between coronary calcium content and increased cardiovascular risk may involve the potential adverse effect of widespread atherosclerosis on vascular function, thereby increasing the potential for coronary vasoconstriction and thrombosis. Our findings demonstrate a rather weak inverse relationship between increasing levels of CAC content and measures of coronary vasodilator function, reflecting atherosclerotic disease activity, both on a per patient and per vessel analysis. In multivariable modeling, including age, body mass index and CAD risk factors, the CAC score remained a modest although statistically significant predictor of the coronary flow reserve. Biologically, these data seem to suggest that coronary calcium content reflects primarily an anatomic measure of atherosclerotic burden. The correlation between CAC content with coronary vascular dysfunction likely reflects the effects of coexisting coronary risk factors on endothelial and microvascular function. (19) These results agree and extend the findings reported by Wang et al (20) by demonstrating the interrelation between the coronary calcification and vasodilator function in symptomatic population with higher clinical risk. These investigators reported the association of CAC and myocardial perfusion as assessed by magnetic resonance imaging during stress and adenosine induced hyperemia in 222 asymptomatic men and women enrolled in the Multi-Ethnic Study of Atherosclerosis. They also reported a modest but significant inverse correlation between CAC score and hyperemic MBF ($r = -0.38$, $p<0.0001$) and perfusion reserve ($r = -0.35$, $p<0.0001$). The

mean hyperemic MBF and mean perfusion reserve were progressively lower with increasing CAC categories.

However, our findings differ from those reported by Pirich et al.(21) demonstrating no significant relationship between coronary calcification and vasoreactivity in a small group of 21 asymptomatic subjects with family history of premature CAD. These investigators reported that CFR, as measured by N-13 ammonia PET, was significantly related to age ($r=0.4$, $p<0.05$) but not to CAC score ($r=0.18$, $p=NS$). There was a significantly higher MBF during stress in subjects with CAC score <100 compared to subjects with CAC >100 (2.55 ± 5.3 vs 1.96 ± 5.2 ml/min/g, $p=0.03$), however no significant difference in CFR was observed between the two groups (3.48 ± 0.55 vs 3.03 ± 0.84 , $p=NS$). The apparent discrepancies with the results of our study may be related to differences in sample size and clinical risk.

Exactly how coronary calcification may affect vasodilator function in humans cannot be determined from this study. However, several potential mechanisms could explain the modest correlation between CAC and microvascular function. First, our results suggest that the inverse correlation between CAC and vasodilator function is explain in part by the coexistence of risk factors that are known to affect endothelial and microvascular function. Indeed, the strength of the association was weakened after adjusting for baseline risk factors in multivariable analysis. Second, it is also possible that coronary calcification reflect more widespread atherosclerosis affecting both epicardial and resistance coronary arteries. It is estimated that for every calcified lesion there are many more non-calcified plaques that may more closely relate to diffuse inflammation of the coronary vasculature affecting vascular endothelial and smooth muscle cell function and hence, coronary vasoreactivity (10). Finally, it is also possible that the observed inverse relationship between calcification and CFR may have been affected by the presence of occult CAD. PET imaging is a sensitive approach for detection of CAD (22-24) Since we excluded patients with known CAD or overt perfusion defects on PET imaging, this is less likely.

Limitations

Our study consisted of an entirely physician referral-based diagnostic population with an intermediate likelihood of CAD. As such, this study design and the nature of patients referred to stress imaging limit the generalizability of our results to screening low risk populations. Larger prospective studies investigating the relationship between myocardial perfusion reserve and coronary calcification could help confirm or extend our findings. Coronary angiography was not routinely performed in our study patients and was clinically unjustified in our patients with normal PET scans, and thus we cannot ascertain the potential effect of epicardial stenoses on flow reserve. However, we excluded patients with known CAD and those with overt stress defects on PET imaging.

Conclusions

In patients with intermediate likelihood but without overt CAD, there is a modest but statistically significant inverse relationship between CAC content and coronary vasodilator function, which persists after adjusting for the effect of coronary risk factors.

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Figure 1. Relationship between coronary artery calcium (CAC) and myocardial blood flow (MBF), coronary flow reserve (CFR) and coronary vascular resistance (CVR) - per patient analysis.

* P < 0.05 on pair-wise comparison

Figure 2.
Relationship between coronary artery calcium (CAC) and myocardial blood flow (MBF), coronary flow reserve (CFR) and coronary vascular resistance (CVR) - per vessel analysis.

Table 1

Characteristics of study patients

Variable	All patients (N=136)
Age (years)	62 ±12
Male gender	44 (32%)
Diabetes	35 (26%)
Hypertension	100 (74%)
Dyslipidemia	85 (63%)
Smoking history	15 (11%)
Family history of premature CAD	53 (39%)
Body mass index (kg/m ²)	33 ±9
Reason for testing	
Chest pain	68 (50%)
Dyspnea	40 (29%)
CAD Likelihood	0.31 ±0.25
Agatston CAC score	249 ±528

CAD = coronary artery disease

Table 2

Systemic hemodynamics

Hemodynamic parameter	All patients (n=136)
Heart rate (bpm)	
rest	72 ±13
stress	84 ±18 *
Systolic blood pressure (mmHg)	
rest	153 ±22
stress	142 ±25 *
Diastolic blood pressure (mmHg)	
rest	73 ±11
stress	65 ±14 *
Mean arterial pressure (mmHg)	
rest	100 ±13
stress	91 ±16 *
Rate pressure product	
rest	10894 ±2521
stress	11927 ±3537 *

*
p<0.0001 compared to rest

Table 3

Myocardial Blood Flow, flow reserve, and coronary vascular resistance

All patients (n=136)	
Myocardial Blood Flow (ml/min/g)	
Baseline	1.0 ±0.2
Hyperemia	1.7 ±0.6 *
Coronary flow reserve	1.7 ±0.5
Coronary Vascular Resistance (mmHg/ml/min/g)	
Baseline	103 ±27
Hyperemia	60 ±22 *

*
p<0.0001 compared to rest

Table 4

Predictors of impaired CFR in the multivariable linear logistic regression analysis.

Multivariable model			
	Parameter estimate	95% confidence interval	P value
Age	– 0.004	–0.011 to 0.004	0.3
Male Gender	– 0.14	Need to rerun in SPSS	0.1
Diabetes	– 0.13	–0.31 to 0.06	0.2
Hypertension	– 0.19	–0.38 to –0.001	0.049 *
Dyslipidemia	0.03	–0.14 to 0.2	0.74
Smoking history	– 0.1	–0.35 to 0.16	0.45
Body mass index	– 0.01	–0.02 to –0.004	0.005 *
CAC score	– 0.0002	Need to rerun in SPSS	0.04 *

*
p<0.05