Quantitative relationship between coronary artery calcium and myocardial blood flow by hybrid rubidium-82 PET/CT imaging in patients with suspected coronary artery disease

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Background. **We assessed the relationship between coronary artery calcium (CAC) score, myocardial blood flow (MBF) and coronary flow reserve (CFR) in patients undergoing hybrid ^{82}Rb positron emission tomography (PET)/computed tomography (CT) imaging for suspected CAD. We also evaluated if CAC score is able to predict a reduced CFR independently from conventional coronary risk factors.**

Methods. **A total of 637 (mean age 58 ± 13 years) consecutive patients were studied. CAC score was measured according to the Agatston method and patients were categorized into 4 groups (0, 0.01-99.9, 100-399.9, and ≥400). Baseline and hyperemic MBF were automatically quantified. CFR was calculated as the ratio of hyperemic to baseline MBF and it was considered reduced when <2.**

Results. **Global CAC score showed a significant inverse correlation with hyperemic MBF and CFR (both $P < .001$), while no correlation between CAC score and baseline MBF was found. At multivariable logistic regression analysis age, diabetes and CAC score were independently associated with reduced CFR (all $P < .001$). The addition of CAC score to clinical data increased the global chi-square value for predicting reduced CFR from 81.01 to 91.13 ($P < .01$). Continuous net reclassification improvement, obtained by adding CAC score to clinical data, was 0.36.**

Conclusions. **CAC score provides incremental information about coronary vascular function over established CAD risk factors in patients with suspected CAD and it might be helpful for identifying those with a reduced CFR. (J Nucl Cardiol 2016)**

Key Words: Coronary artery calcium • myocardial blood flow • coronary flow reserve • PET/CT • coronary artery disease

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Abbreviations	
CAC	Coronary artery calcium
CAD	Coronary artery disease
CFR	Coronary flow reserve
MBF	Myocardial blood flow
PET	Positron emission tomography
CT	Computed tomography
LAD	Left anterior descending artery
LCx	Left circumflex artery
RCA	Right coronary artery

INTRODUCTION

The presence of coronary artery calcium (CAC) is indicative of atherosclerosis and calcium content demonstrates a good correlation with the overall coronary atherosclerotic burden.[1-3] However, calcium deposits do not completely reflect overall disease activity within the coronary circulation and direct measures of coronary vasodilator function may be more powerful measures of coronary artery disease (CAD) risk.[4] A significant inverse relationship between CAC content and both hyperemic myocardial blood flow (MBF) and coronary flow reserve (CFR) has been demonstrated.[5–7] Yet, in patients with low to intermediate pre-test likelihood of CAD and without obstructive disease at invasive or CT-based coronary angiography these relationships disappeared after adjusting for conventional risk factor.[8] In the present study, we used ^{82}Rb positron emission tomography (PET)/computed tomography (CT) imaging to quantitatively assess in a large cohort of patients with suspected CAD the relationship between CAC score and coronary vascular function and to evaluate if CAC score is able to predict a reduced CFR independently from conventional coronary risk factors.

METHODS

Patients

The study population comprised 637 subjects referred to CAC scoring and PET/CT MBF measurements for atypical cardiac chest pain or dyspnea. For each patient the presence of coronary risk factors were noted. Hypertension was defined as a blood pressure ≥140/90 mmHg or the use of anti-hypertensive medication.[9] Hypercholesterolemia was defined as total cholesterol level ≥6.2 mmol/L or treatment with cholesterol lowering medication. Patients were classified as having diabetes if they were receiving treatment with oral hypoglycemic drugs or insulin. A positive family history of CAD was defined by the presence of disease in first-degree relatives younger than 55 years in men or 65 years in women. Exclusion criteria were documented history of CAD defined as previous percutaneous coronary intervention, coronary artery bypass graft surgery, or myocardial infarction. Patients with uncontrolled atrial fibrillation, pacemaker, or prosthetic valve were also excluded.

PET Imaging

As a routine preparation for ^{82}Rb cardiac PET/CT, patients were asked to discontinue taking nitrates for 6 hours, calcium channel blockers and caffeine-containing beverages for 24 hours, and b-blockers for 48 hours before their appointment. Scans were acquired using a Biograph mCT 64-slice scanner (Siemens Healthcare). Rest and stress cardiac PET/CT images were acquired as follows: scout CT to check the patient position and low-dose CT (0.4 mSv; 120 kVp; effective tube current, 26 mA [11-mAs quality reference]; 3.3 seconds) were performed for attenuation correction, during normal breathing before and after PET acquisitions. For both rest and stress images 1110 MBq of ^{82}Rb were injected intravenously and a 6-minute list-mode PET study was acquired. Pharmacologic stress was then administered using adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4.5 minutes). Both rest and stress dynamic images were reconstructed into 26 time frames (12 × 5 seconds, 6 × 10 seconds, 4 × 20 seconds, and 4 × 40 seconds; total, 6 minutes) using the vendor standard ordered-subsets expectation maximization 3D reconstruction (2 iterations, 24 subsets) with 6.5-mm gaussian post-processing filter.

Regional myocardial perfusion was visually assessed, using standardized segmentation of 17 myocardial regions. Each myocardial segment was scored from normal (score = 0) to absent perfusion (score = 4). The summed stress score was obtained by adding the scores of the 17 segments of the stress images. A similar procedure was applied to the resting images to calculate the summed rest score and summed difference score was the difference between the stress and rest scores. Myocardial perfusion was considered abnormal when summed stress score was ≥3. Subjects with summed difference score ≥2 were defined as having stress-induced myocardial ischemia (2-6 mild ischemia and >6 moderate-severe ischemia).

Absolute MBF (in $mL \cdot min^{-1} \cdot g^{-1}$) was computed from the dynamic rest and stress imaging series with commercially available software (Siemens Syngo Dynamic PET).[10] In addition to calculating the MBF for the left ventricle as a whole, MBF was calculated for each of three coronary vascular territories: left anterior descending (LAD), left circumflex (LCx), and right (RCA) coronary arteries.[11] CFR was defined as the ratio of hyperemic to baseline MBF and was considered reduced when <2.[12]

CT Imaging

All patients underwent a CT scan for CAC scoring. Those with heart rate >75 bpm received prior intravenous beta-blockers (5-10 mg atenolol). A standard scanning protocol was applied, with 18 mm section collimation (30 × 0.6 mm), 0.24 ms gantry rotation time, 120 kVp tube voltage, and 60 Q ref mAs tube current. CAC scoring was obtained during a single breath hold and coronary calcification was defined as a plaque with an area of 1.03 mm^2 and a density ≥130 HU. The CAC score was calculated according to the method described by Agatston.[13] Experienced nuclear medicine physicians analyzed the CT, blinded to the PET results (Siemens, Syngo Multi-modality Workplace). CAC scores were calculated separately for the LAD, LCx, and RCA coronary arteries and summed to provide a total CAC score.

Likelihood of CAD

Prescan likelihood of CAD was calculated by dedicated software (Cadenza, Advanced Heuristics Inc., Bainbridge Island, Washington).[14] The likelihood of CAD was analyzed as aggregate descriptors of clinical data based on Bayesian analysis of the following patient variables: age, gender, blood pressure, smoking history, serum cholesterol level, glucose intolerance, family history of CAD. Prescan likelihood of CAD was considered low when <0.15, intermediate between 0.15 and 0.85, and high when >0.85.[15]

Statistical Analysis

Categorical variables are expressed as count and percentage and continuous variables as mean values ± standard deviation. The normality of continuous data was visually inspected using the normal quantile plot and standardized normal probability plot, and formally assessed using the Shapiro-Wilk test. The ln(CAC + 1) score transformation was used to adjust for the rightward skew of the data and to reduce heteroscedasticity. Evaluation of relationships between ln(CAC + 1) score and both MBF and CFR was performed using Spearman's rank correlation analysis. CAC score was also categorized into 4 groups (0, 0.01-99.9, 100-399.9, and ≥400). Differences in MBF and CFR across levels of CAC score were assessed using the Kruskal-Wallis rank test, also checking for nonparametric trend in the presence of statistical significance. Univariable and multivariable linear regression analyses were performed to examine the relationship between age, gender, cardiac risk factors, ln(CAC + 1) score and MBF and CFR. We considered for the multivariable analysis only variables statistically significant at univariable analysis. The normality of residuals was graphically assessed comparing the kernel density estimate with the normal distribution with the same mean and standard deviation. Univariable and multivariable logistic regression analyses were also performed to identify the variables associated with a reduced CFR. For this latter analysis two different models were considered: model 1 included clinical data significant at univariable analysis and model 2 clinical data and CAC score. The incremental value of model 2 over model 1 was assessed by the likelihood ratio chi-square. Finally, to evaluate whether CAC score is able to reclassify patients with reduced CFR, the continuous net reclassification improvement (NRI) was calculated using the formula proposed by Pencina et al[16] Statistical analysis was performed with Stata 14 software (StataCorp, College Station, Texas USA). A P value <.05 (two-sided) was considered statistically significant.

RESULTS

Clinical characteristics of the 637 patients included are shown in Table 1. In the overall patient population 534 (84%) patients were at low and 103 (16%) at intermediate pre-test likelihood of CAD. CAC score was zero in 288 (45%) patients, 0.1-99.9 in 137 (22%), 100-399.9 in 95 (15%), and ≥400 in 117 (18%). The large majority (n = 583) of patients had normal myocardial perfusion, while 54 showed stress-induced mild ischemia. The distribution of patients with normal or abnormal myocardial perfusion across CAC categories is depicted in Figure 1. Overall global baseline MBF was 1.2 ± 0.39 mL × min^{-1} × g^{-1}. During adenosine-induced hyperemia, MBF increased significantly to 2.75 ± 0.80 mL × min^{-1} × g^{-1} (P < .001 vs baseline) and CFR averaged 2.45 ± 0.73. The prevalence of reduced CFR according to risk factors is shown in Table 2.

Relation Between CAC Score and Coronary Vascular Function

Spearman's rank correlations of global baseline MBF, hyperemic MBF, and CFR with ln(CAC + 1) score were 0.027 (P = .49), −0.303 (P < .001), and −0.349 (P < .001), respectively. Mean values of baseline and hyperemic MBF and CFR according to CAC categories are depicted in Figures 2 and 3. As illustrated, baseline MBF was comparable among patients at different levels of CAC score (2.74, P = .433). On the other hand, hyperemic MBF (62.97, P < .001) and CFR (78.22 P < .001) progressively decreased with increasing CAC levels (both P for nonparametric trend < .001). Noteworthy, only the group of patients with a CAC score ≥400 (n = 117) had an average CFR below normal and 38 (32%) of them were diabetics.

For individual coronary vascular territories, Spearman's rank correlations of baseline MBF, hyperemic

Table 1. Patient characteristics

Age (years)	58 ± 13
Male gender	330 (47%)
Body mass index (kg·m^{-2})	32 ± 7
Diabetes	132 (21%)
Hypertension	371 (58%)
Dyslipidemia	363 (57%)
Smoking history	121 (19%)
Family history of CAD	333 (52%)
ln(CAC + 1) score	2.7 ± 2.7
Abnormal perfusion	54 (8%)

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects
CAD, coronary artery disease; *CAC*, coronary artery calcium

MBF and CFR with ln(CAC + 1) score were 0.037 (P = .49), −0.263 (P < .001), and −0.309 (P < .001) for LAD; −0.046 (P = .40), −0.303 (P < .001), and −0.204 (P < .001) for LCx; −0.026 (P = .64), −0.283 (P < .001), and −0.283 (P < .001) for RCA.

Linear regression analyses considering as dependent variables hyperemic MBF and CFR are reported in Tables 3 and 4, respectively. As shown, at multivariable linear regression analysis age, male gender, diabetes, and ln(CAC + 1) score were inversely related with both hyperemic MBF and CFR. For the coefficients reported in multivariable linear regression analyses, it appears that for any 10% increase in CAC score the average hyperemic MBF reduces 0.003 (i.e., $-0.034 \times \ln(1.1) = -0.003$) and the average CFR reduces 0.005 (i.e., $-0.053 \times \ln(1.1) = -0.005$). The residual plots appear to be close to the normal distribution for both CFR and hyperemic MBF regression (Figure 4).

Predictors of Reduced CFR

Univariable and multivariable logistic regression analyses with reduced CFR as dependent variable are reported in Table 5. At multivariable analysis age, diabetes, and CAC score ≥400 were independently associated with a reduced CFR. Compared with subjects with a CAC score of zero, the age- and diabetes-adjusted odds ratios for reduced CFR were 1.52 [95% confidence interval (CI) 0.91-2.56)], 1.42 (95% CI 0.78-2.36), and 2.62 (95% CI 1.49-4.61) for those with a CAC score of 0.1-99.9, 100-399.9, and ≥400, respectively. Similarly, when only patients with normal myocardial perfusion (n = 583) were considered age, diabetes, and CAC score ≥400 were independently associated (all P < .01) with a reduced CFR at multivariable analysis.

The conditional marginal effects of diabetes on the probability of reduced CFR by multivariable logistic regression analysis, for the different calcium score categories at age 40 y and age 70 y are illustrated in Figure 5. As shown, diabetic patients had a higher probability of reduced CFR at any level of calcium score category as compared to non-diabetic subjects, without

Table 2. Prevalence of reduced CFR according to risk factors

Risk factor	Prevalence
Diabetes	58 (44%)
Hypertension	122 (33%)
Dyslipidemia	105 (29%)
Smoking history	35 (29%)
Family history of CAD	80 (24%)

Values are expressed as number (percentage) of subjects
CAD, coronary artery disease

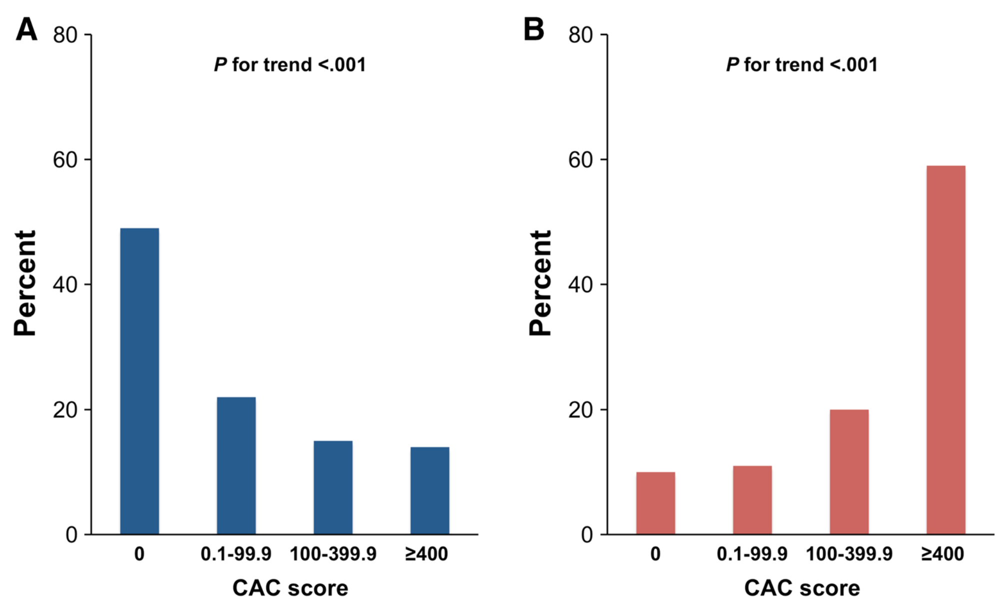

Figure 1. Bar graphs illustrating the distribution (%) of patients with normal (n = 583) (**A**) or abnormal (n = 54) (**B**) myocardial perfusion across the different CAC score categories.

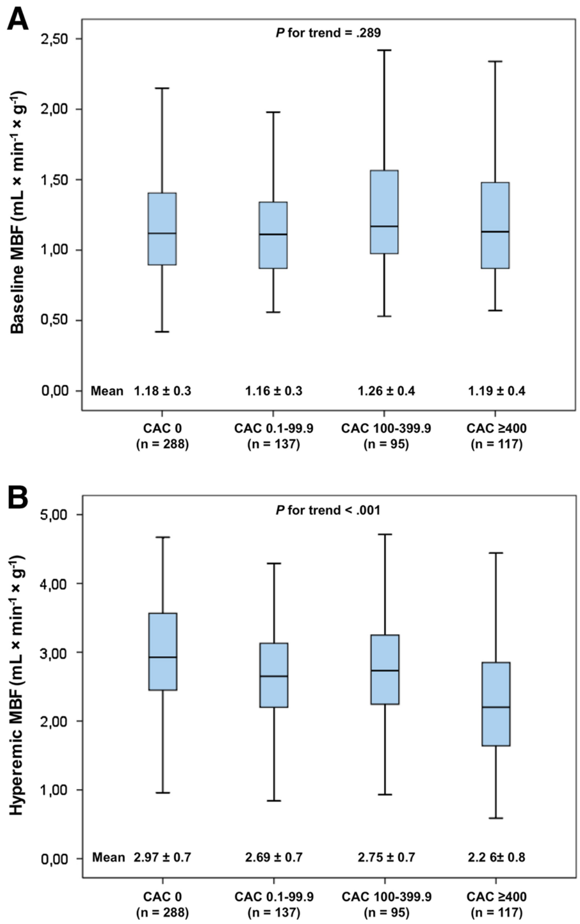

Figure 2. Box plots of baseline (**A**) and hyperemic (**B**) myocardial blood flow (MBF) according to coronary artery calcium (CAC) score categories.

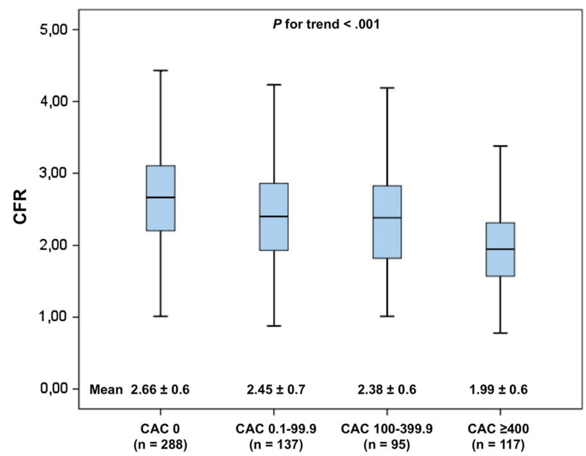

Figure 3. Box plots of coronary flow reserve (CFR) according to coronary artery calcium (CAC) score categories.

interaction between diabetes and the categories of calcium score. Overall, the number of diabetics was 49 (17%) in subjects with a CAC score of zero, 24 (17%) in those with a CAC score of 0.1-99.9, 21 (22%) in those with CAC score 100 to 399.9 and 38 (32%) in those with CAC score ≥400, respectively. The addition of CAC score to clinical data, increased the global chi-square value for predicting reduced CFR from 81.01 to 91.13 ($P < .001$). The continuous NRI by adding CAC score to clinical data was 0.36 (95% bootstrap CI 0.32-0.39). In particular, continuous NRI was 0.19 for patients with reduced CFR and 0.17 for those with normal CFR.

Table 3. Linear regression analyses with hyperemic MBF as dependent variable

	Univariable analysis			Multivariable analysis		
	β coefficient	SE	*P* value	β coefficient	SE	*P* value
Age	−0.017	0.002	<.001	−0.013	0.003	<.001
Male gender	0.409	0.062	<.001	0.360	0.062	<.001
Body mass index	0.000	0.004	0.958			
Diabetes	−0.358	0.077	<.001	−0.267	0.075	<.001
Hypertension	−0.183	0.064	0.004	−0.043	0.064	0.536
Dyslipidemia	−0.133	0.064	0.039	0.028	0.063	0.682
Smoking history	−0.032	0.081	0.693			
Family history of CAD	0.188	0.063	0.003	0.136	0.059	0.021
ln(CAC + 1) score	−0.086	0.011	<.001	−0.034	0.013	0.008

SE, standard error; *CAD*, coronary artery disease; *CAC*, coronary artery calcium

Table 4. Linear regression analyses with CFR as dependent variable

	Univariable analysis			Multivariable analysis		
	β coefficient	SE	*P* value	β coefficient	SE	*P* value
Age	−0.022	0.002	<.001	−0.014	0.003	<.001
Male gender	−0.122	0.058	0.034	−0.094	0.055	<.001
Body mass index	0.001	0.004	0.814			
Diabetes	−0.321	0.070	<.001	−0.266	0.065	<.001
Hypertension	−0.239	0.058	<.001	−0.084	0.055	0.111
Dyslipidemia	−0.099	0.058	0.091			
Smoking history	0.044	0.074	0.554			
Family history of CAD	0.115	0.058	0.053			
ln(CAC + 1) score	−0.086	0.010	<.001	−0.053	0.012	<.001

SE, standard error; *CAD*, coronary artery disease; *CAC*, coronary artery calcium

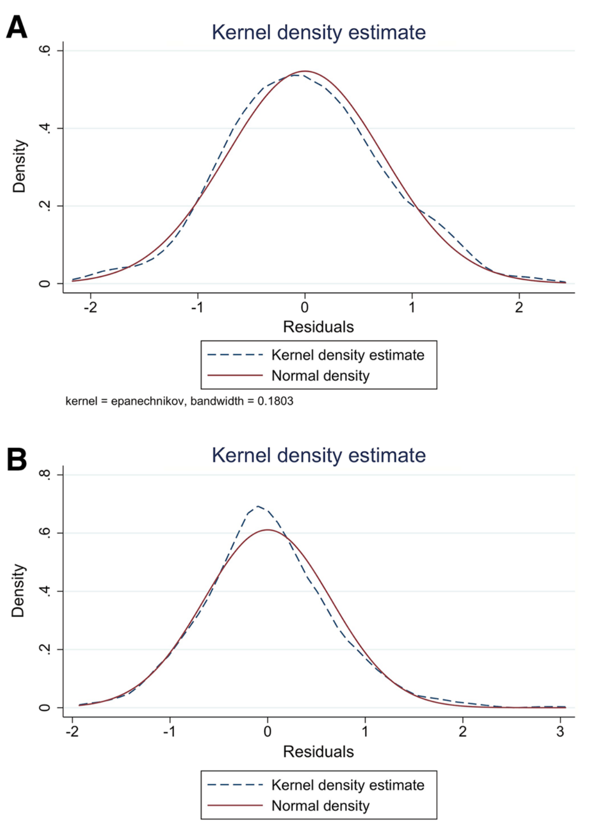

Figure 4. Kernel density estimate of residuals of multivariable linear regression analysis for hyperemic MBF (**A**) and CFR (**B**).

DISCUSSION

From this study, performed in a large cohort of patients with suspected CAD, it emerged a negative correlation between the extent of CAC and coronary vascular function, while no relation between resting MBF and CAC was detectable. The addition of CAC score to clinical data showed an incremental value over established CAD risk factors in predicting a reduced CFR.

Our results confirm in a larger patient population those of previous reports.[5–8] Currillova et al[5] studied 136 patients without known CAD and normal myocardial perfusion and found an inverse relationship between CAC and both hyperemic MBF and CFR by ^{82}Rb PET, in per patient and per vessel analyses. This relationship remained also after adjusting for coronary risk factors. Wang et al,[6] evaluating by magnetic resonance imaging 222 asymptomatic patients without documented CAD and showed that coronary vasodilator response was inversely associated with presence and severity of CAC, independently from cardiovascular risk factors. More recent data on the quantitative relationship between CAC score and MBF assessed by hybrid ^{15}O-water PET/TC in a group of 173 patients without a documented history of CAD and without obstructive coronary artery disease, confirmed the inverse relationship between CAC and hyperemic MBF and CFR.[8] However, this association disappeared after adjustment for traditional risk factors. Thus, the authors concluded that CAC does not add incremental value regarding coronary vascular function over established CAD risk factors in the absence of obstructive epicardial disease. However, in the work-up of suspected CAD assessing calcium score is preliminary to CT-based and/or invasive coronary angiography. Thus, selecting for the analysis only patients without obstructive CAD might bias the generalizability of the results. However, in our study when only patients with normal myocardial perfusion were considered CAC score still independently predicted a reduced CFR.

Table 5. Logistic regression analyses with reduced CFR as dependent variable

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	***P* value**	**Odds ratio (95% CI)**	***P* value**
Age	1.059 (1.042-1.076)	<.001	1.043 (1.023-1.062)	<.001
Male gender	1.167 (0.823-1.655)	0.386		
Body mass index	0.988 (0.963-1.013)	0.328		
Diabetes	0.389 (0.261-0.581)	<.001	0.430 (0.278-0.664)	<.001
Hypertension	0.520 (0.359-0.752)	<.005	0.785 (0.524-1.175)	0.239
Dyslipidemia	0.859 (0.604-1.223)	0.400		
Smoking history	0.924 (0.596-1.432)	0.723		
Family history of CAD	1.460 (1.030-2.069)	0.034		
CAC score 0 (reference group)	1		1	
CAC score 0.1-99.9	2.094 (1.287-3.407)	0.003	1.521 (0.907-2.552)	0.112
CAC score 100-399.9	2.428 (1.422-4.147)	0.001	1.418 (0.787-2.554)	0.244
CAC score ≥400	5.731 (3.544-9.266)	<.001	2.619 (1.488-4.610)	0.001

CAD, coronary artery disease; *CAC*, coronary artery calcium

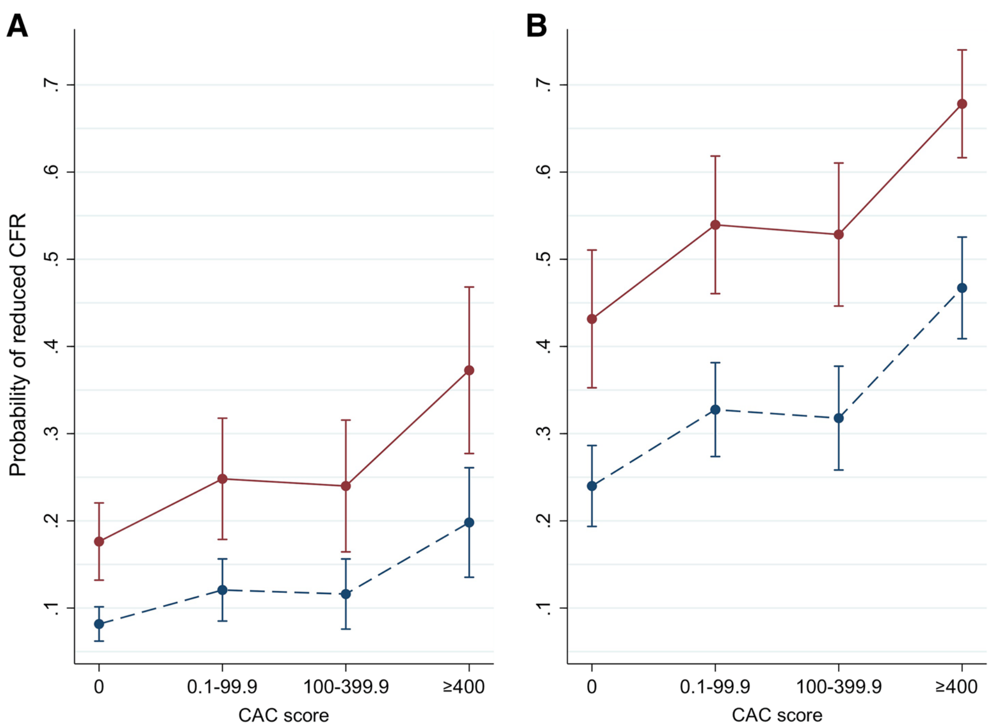

Figure 5. Conditional marginal effects of diabetes (*red solid lines* diabetes; *blue dashed lines* no diabetes) on the probability of reduced coronary flow reserve (CFR) by multivariable logistic regression analysis, for the different calcium score categories at age 40 years (**A**) and age 70 years (**B**).

The correlation between CAC content and coronary vascular dysfunction reflects the effects of coexisting coronary risk factors on endothelial and microvascular function.[5,6] Interestingly, in our study ln(CAC + 1) score remained inversely related to both hyperemic MBF and CFR also after adjusting for cardiovascular risk factors. However, considering CAC score categories, only a CAC score ≥400 was significantly associated with a reduced CFR. The weak association between CAC score <400 and reduced CFR suggests that calcium deposits are not a complete reflection of overall disease activity within the coronary circulation, supporting the hypothesis that measures of coronary vasodilator function may be more powerful measures of CAD risk than simply the total burden of calcified atherosclerosis. The absence of correlation between CAC score and resting MBF is not surprising because it has been widely demonstrated that basal MBF remains constant despite any increase in the severity of coronary artery stenosis.[17] From our data it also emerged that diabetic patients showed a higher probability of reduced CFR as compared to non-diabetic patients in all CAC categories. This result is in agreement with the finding of a lower increase in hyperemic MBF in diabetic patients as compared to non-diabetic subjects.[18]

NEW KNOWLEDGE GAINED

CAC scoring is commonly used in clinical practice, but its ability in predicting coronary vascular dysfunction is still debated. In the clinical setting the evaluation of subjects with suspected CAD assessing calcium score is preliminary to CT-based and/or invasive coronary angiography. Our findings indicate that a high CAC score is associated with coronary vascular dysfunction and reduced CFR. Of note, CAC score is able to predict a reduced CFR also in patients with normal myocardial perfusion.

CONCLUSION

In patients without known CAD there is a significant inverse relationship between extent of CAC and coronary vascular function. Age, diabetes, and CAC score independently predict a reduced CFR. CAC score also provides incremental information over established CAD risk factors for predicting coronary vascular dysfunction.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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