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Dipartimento di Scienze Biomediche Avanzate
Direttore: Prof. Claudio Buccelli

Dottorato di Ricerca in "Scienze Biomorfologiche e Chirurgiche"

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Coordinatore: Prof. Alberto Cuocolo

Tesi di Dottorato

Prognostic value of quantitative coronary artery calcium and myocardial blood flow assessed by hybrid rubidium-82 PET/CT imaging in patients with suspected coronary artery disease

Relatore
Ch.ma Prof. Wanda Acampa

Candidata
Dott.ssa Roberta Assante

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Introduction

Noninvasive diagnosis of coronary artery disease (CAD) and risk assessment represents major challenge for clinical decision-making in patients with suspected CAD (1). Coronary artery calcium (CAC) score evaluation demonstrated to have a significant role in appropriate management of patients with suspected CAD (2). In particular, CAC scoring resulted as a powerful tool in risk-stratifying asymptomatic patients at intermediate risk of CAD (3). It has been also demonstrated that not only the presence but also the extent of coronary calcification significantly improve the prediction of cardiovascular events in addition to traditional cardiovascular risk factors (4). Myocardial perfusion imaging (MPI) with positron emission tomography (PET)/computed tomography (CT) allows absolute quantification of myocardial blood flow (MBF) and coronary flow reserve (CFR) with a feasible possibility to perform CAC quantification as a part of the same examination (5). Different published data have demonstrated that the presence of abnormal CFR by PET using different tracers, reflecting both the presence of epicardial coronary artery stenosis and microvascular dysfunction, was significantly associated with a higher cardiac event rate in patients with suspected and known CAD (6,7). Thus, recently some studies evaluated the

combined role of structural and functional information obtained by PET/CT in the

evaluation of patients with suspected or known CAD (8,9). In particular, a significant

inverse relationship between extent of CAC and CFR by rubidium-82 (^{82}Rb) PET/CT has

been observed in patients with suspected CAD (9). However, few data are available

combining measures of structural abnormalities and coronary vasodilator function by ^{82}Rb

PET/CT in predicting adverse cardiac events. Thus, aim of this study was to evaluate the

long-term prognostic value of CAC score and MBF by hybrid ^{82}Rb PET/CT imaging in a

cohort of patients with low-intermediate risk of CAD.

Methods

Patient population

The study population comprised 295 subjects referred to CAC scoring and MBF measurements by PET/CT for atypical cardiac chest pain. For each patient the presence of coronary risk factors was noted. Hypertension was defined as a blood pressure ≥140/90 mmHg or the use of anti-hypertensive medication (10). 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 x 5 seconds, 6 x 10 seconds, 4

x 20 seconds, and 4 x 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 (11). 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

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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·min-1·g-1) was computed from the dynamic rest and stress imaging series with commercially available software (Siemens Syngo Dynamic PET) (12). CFR was defined as the ratio of hyperemic to baseline MBF and was considered reduced when <2 (13).

CT imaging

All patients underwent a CT scan for CAC scoring. Those with heart rate >75 bpm received prior intravenous betablockers (5-10 mg atenolol). A standard scanning protocol was applied, with 18 mm section collimation (30 9 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 (14). Experienced nuclear medicine physicians analyzed the CT, blinded to the PET results (Siemens, Syngo Multimodality Workplace). CAC scores were calculated

separately for the LAD, LCx, and RCA coronary arteries and summed to provide a total CAC score. CAC score was also categorized into 3 groups (0,1-399 and ≥400).

Follow-up data

Patient follow-up was prospectively obtained by use of a questionnaire that was assessed by a phone call to all patients and general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The outcome was a composite end point of cardiac death, nonfatal myocardial infarction, or unstable angina requiring coronary revascularization whichever occurred first. The cause of death was confirmed by review of death certificate, hospital chart, or physician's records. Death was considered to be of cardiac origin if the primary cause was defined as acute myocardial infarction, congestive heart failure, valvular heart disease, sudden cardiac death, cardiac interventional/surgical procedure related. Myocardial infarction was defined when >2 of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes (15). The date of the last examination or consultation was used to determine the length of follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. Comparison between groups was performed with unpaired t test and Chi-square test as appropriate. A P value <.05 was considered statistically significant. The ln(CAC+1) score transformation was used to adjust for the rightward skew of the data and to reduce heteroscedasticity. Survival analysis was performed by univariable and multivariable Cox proportional hazard regression analysis. Only variables showing a P value <.05 at univariable analysis were considered for multivariable analysis. Event-free survival curves were obtained by the Kaplan-Meier method and compared with the log-rank test. The incremental prognostic value of clinical data and imaging findings was assessed considering variables in hierarchical order. To address the incremental prognostic value of CAC score, we added CAC score to a model including only clinical variables (model 1) to obtain an adjusted hazard ratio for CAC (model 2). Moreover, to evaluate incremental prognostic value of CFR, we added CFR to a model 2, including clinical data and CAC score. All the analyses were performed using STATA version 14.0 for Windows (StataCorp LP, College Station, TX).

Results

Patient Characteristics and Outcome

Of the 295 patients enrolled, follow-up data were not available in 26 patients (8%). The median follow-up was 48±18 months. During follow-up, 17 events occurred (6% cumulative event rate). The events were cardiac death in 3 patients, nonfatal myocardial infarction in 3 and unstable angina requiring revascularizations in 11. Clinical characteristics of patients with and without events were reported in Table 1. Patients who experienced event were older and showed higher prevalence of hypertension and dyslipidemia and a higher BMI value as compared to patients without event. Of the overall patients, normal myocardial perfusion was observed in 238 (88%) patients, while 31 (12%) patients showed stress-induced mild ischemia. In particular, the prevalence of abnormal MPI was significantly higher in patients with events as compared to those without (41% vs 9%, respectively P <.001). Coronary artery calcium and vascular function of the overall patients were reported in Table 2. As showed patients who experienced event showed a higher ln(CAC + 1) and a lower CFR values as compared to patients without event, while no differences has been observed in baseline and hyperemic MBF between the two groups. Moreover, patients with event had a lower prevalence of CAC score 0 and a higher

prevalence of CAC ≥400 as compared to patients without events. On the contrary, the

prevalence of CAC score 1-399 was not significantly different between the two groups.

Event rate in both CAC score and CFR categories was illustrated in Table 3. As shown,

event rate significantly increased with increasing of CAC score categories (P for trend =

.000) and it was higher in patients with reduced CFR (P = .001).

Predictors of events

Univariable and multivariable Cox regression analyses were reported in Table 4. As shown,

age (P = .01), diabetes (P = .04), hypertension (P = .03), dyslipidemia (P = .02), CAC score

(P = .002) and CFR (P = .000) were predictors of events. Moreover, at multivariable

analysis CAC score ≥400 (P = .007) and CFR (P = .03) were independent predictors of

events. The event-free survival curves according to CAC score categories and CFR were

reported in Figure 1 and 2. As illustrated, event-free survival decreased with worsening of

CAC score category (P <.001) and in patients with reduced CFR (P <.005). The results of

incremental analysis were reported in Figure 3. CAC score added prognostic information to

a model including in hierarchical order clinical variables, increasing the global chi-square

from 21.65 to 28.78 (P = .005). Moreover, the addition of CFR to a model including clinical

data and CAC score further significantly increased global chi-square from 28.78 to 34.76 (P

= .002).

Discussion

From this study it emerged that both the extent of coronary calcification and the presence of coronary vascular dysfunction by ^{82}Rb cardiac PET/CT are associated with increased risk of adverse cardiac events, even after adjustment for cardiovascular risk factors. In particular, the presence of CAC score ≥400 and CFR resulted as independent predictors of events.

The presence of CAC score is indicative of the overall coronary atherosclerotic burden and is a strong predictor of cardiac events, as investigated in several studies (16,17). In particular, it has been demonstrated a very low rate of cardiovascular events among patients with CAC score of zero (16) while event rate increase incrementally according to CAC score among those with abnormal CAC scans (17). In a large cohort of asymptomatic patients, Budoff et al. (17) have demonstrated that the increase of plaque burden is associated with increasing risk, supporting evidence that there is a relationship between the extent of CAC and all-cause mortality. Moreover, when CAC score was added to risk factors provided incremental information for predicting outcomes (18). In a large study population with suspected CAD, CAC score has demonstrated to provide the highest improvement in the prediction of event over the other cardiovascular risk markers,

suggesting the use of CAC as a powerful tool for improving cardiovascular risk prediction

in individuals classified as intermediate risk (18). PET imaging is a noninvasive procedure

with the potential for absolute quantification of MBF and CFR as markers of coronary

vascular function, and several studies have demonstrated the prognostic role of PET-derived

flow reserve in subjects with and without known CAD (7,19). In particular, inclusion of

CFR in the risk prediction models provided incremental risk stratification beyond clinical

and perfusion variables and resulted in a significant incremental risk reclassification of

patients with known or suspected CAD (19). Moreover, the incremental prognostic value of

CFR over standard relative MPI in predicting outcomes it has been widely outlined (20). A

combined evaluation of CAC score and coronary vascular function could significantly

change clinical management of patient with suspected CAD. Dikic et al. (21) in a cohort of

asymptomatic diabetic patients, demonstrated that both CAC score and coronary flow

velocity reserve obtained by MSCT and by transthoracic Doppler echocardiography

assessments respectively, provide independent and complementary prognostic information.

A combined use of the two parameters improved the risk stratification ability and identified

patients at higher risk who could benefit from more aggressive treatment (21). A principal

advantage of hybrid PET/CT is its potential ability to evaluate both the coronary

atherosclerotic burden as assessed by CAC score and coronary vascular function as CFR in a same examination. However, only few data are available about the use of combined measure of structural abnormalities and coronary vasodilator function by [82]Rb PET/CT in predicting adverse cardiac events. In a previous study, Naya et al. (22) in a cohort of 901 symptomatic patients with suspected CAD, undergoing [82]Rb PET/CT, and followed for a median of 1.53 years, demonstrated that both the extent of coronary calcium deposits and the presence of coronary vascular dysfunction are associated with increased risk of adverse cardiac events. However, after adjustment for clinical risk only coronary vascular dysfunction improved risk assessment, confirming that total burden of coronary calcium deposits was only modestly associated with impaired vascular function. They concluded that direct measures of coronary vasodilator function might be more powerful marker of cardiac risk than simply the total burden of calcified atherosclerosis. To the best of our knowledge this is the first study assessing the long-term (48±18 months) prognostic value of combining measures of structural abnormalities and coronary vasodilator function by [82]Rb PET/CT to predict adverse cardiac events in subjects with suspected CAD. Recently, the presence of negative correlation between the extent of coronary calcification and coronary vascular function has been demonstrated in a similar cohort of patients (3). In particular, CAC score

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≥400 resulted associated with coronary vascular dysfunction and reduced CFR reflecting the effects of coexisting coronary risk factors on endothelial and microvascular function (3). Interestingly in the present study both CAC score ≥400 and CFR were significant predictors of cardiac events. Moreover, the results of our study showed that event-free survival decreased with worsening of CAC score categories and it was worse in patients with reduced CFR. Finally, we evaluated incremental prognostic value of CFR in predicting cardiac adverse events. In our study CAC score added prognostic information to a model including in hierarchical order clinical variables. The addition of CFR to a model including clinical data and CAC score further significantly increased the prognostic power of the model. Our work has important clinical implications, suggesting that a combined evaluation of functional and structural abnormalities by hybrid [82]Rb PET/CT imaging might be a potential screening tool to identify patients with low-intermediate risk of CAD at higher risk of cardiac event during at long-term follow-up.

Conclusions

In patients with suspected CAD both the extent of coronary calcification and the presence of coronary vascular dysfunction are associated with increased risk of adverse cardiac events, even after adjustment for cardiovascular risk factors. CAC score≥400 and CFR resulted both as independent predictors of events. However, CFR provides incremental prognostic information over established CAD risk factors and CAC score for predicting cardiac adverse events. Combined evaluation of functional and structural abnormalities might allow risk stratification in patients with low-intermediate risk of CAD.

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Table 1. Clinical characteristics of patients with and without events

	All	Events	No events	P value
	(n=269)	(n=17)	(n=252)	
Age	57 ± 14	64 ± 11	57 ± 14	.037
Male Gender	138(51%)	10(59%)	128(50%)	.521
BMI	30 ± 6	34 ± 9	30 ± 6	.014
Diabetes	53(19%)	6(35%)	47(18%)	.095
Hypertension	174(65%)	15(88%)	159(63%)	.036
Dyslipidemia	147(55%)	14(82%)	133(53%)	.018
Smoking history	69(26%)	2(12%)	67(26%)	.176
Family history of CAD	128(47%)	11(65%)	117(46%)	.144

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects

CAD, coronary artery disease; *BMI,* body mass index

Table 2. Coronary artery calcium and vascular function

	All	Events	No events	P value
	(n=269)	**(n=17)**	**(n=252)**	
Ln(CAC+1) score	2.43±2.83	5.28±2.23	2.24±2.77	.000
CAC categories				
0	141(52%)	1 (6%)	140 (55%)	.000
1-399	77(29%)	6 (35%)	71 (28%)	.694
≥400	51(19%)	10 (59%)	41 (16%)	.000
Hyperemic MBF	2.56±0.89	2.25 ±0.93	2.58 ±0.89	.133
Rest MBF	1.10 ±0.41	1.25 ±0.42	1.09 ±0.40	.137
CFR	2.47 ±0.75	1.84 ±0.48	2.52 ±0.75	.000
CFR<2	105(39%)	13 (76%)	92 (36%)	.001

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects.

CAC, coronary artery calcium; *MBF*, myocardial blood flow; *CFR*, coronary flow reserve.

Table 3. Adverse cardiac events according to coronary artery calcium (CAC) score and coronary flow reserve (CFR)

	Patients (n)	Events (%)
CAC score categories		
0	141	0.7%
1-399.9	77	8%
≥400	51	20%
Coronary flow reserve		
CFR>2	164	2%
CFR<2	105	12%

CAC, coronary artery calcium; *CFR*, coronary flow reserve.

Table 4. Univariable and multivariable predictors of cardiac events

	Univariable analysis		Multivariable analysis	
	Hazard ratio (CI)	***P* value**	**Hazard ratio (CI)**	***P* value**
Age	1.048 (1.008-1.090)	.018	0.984 (0.935-1.035)	.984
Male Gender	0.696 (0.265-1.829)	.462		
BMI	1.021 (1.010-1.138)	.023	1.049 (0.977-1.128)	.188
Diabetes	2.812 (1.036-7.636)	.043	0.979 (0.340-2.825)	.969
Hypertension	4.958 (1.132-21.717)	.034	2.393 (0.536-10.679)	.253
Dyslipidemia	4.242 (1.219-14.766)	.023	2.114 (0.561-7.971)	.269
Smoking history	0.421 (0.096-1.842)	.421		
Family history of CAD	1.217 (0.819-5.999)	.117		
CAC score 0(reference)		.002		.016
CAC score 1-399	11.909 (1.433-98.985)	.022	7.985 (0.903-70.623)	.062
CAC score ≥400	30.279 (3.873-236.698)	.001	21.187 (2.293-195.781)	.007
CFR	0.213 (0.092-0.495)	.000	3.738 (1.096-12.750)	.035

BMI, body mass index; *CAD*, coronary artery disease; *CAC*, coronary artery calcium; *CFR*, coronary flow reserve.
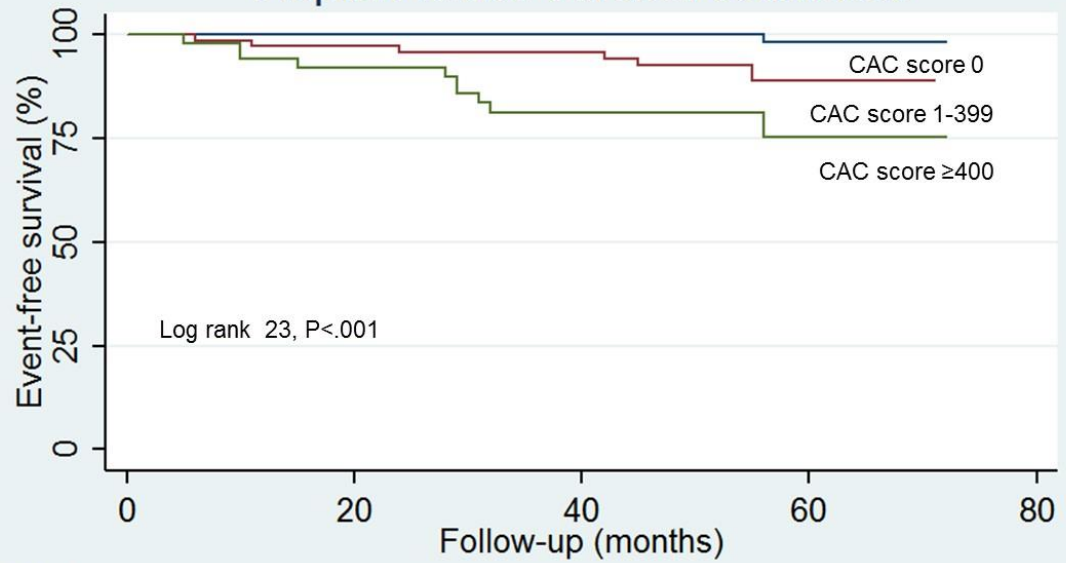
Figure Legends

Figure 1. Event-free survival curves by Kaplan-Meier analysis according to CAC score categories

Figure 2. Event-free survival curves by Kaplan-Meier analysis according to CFR categories
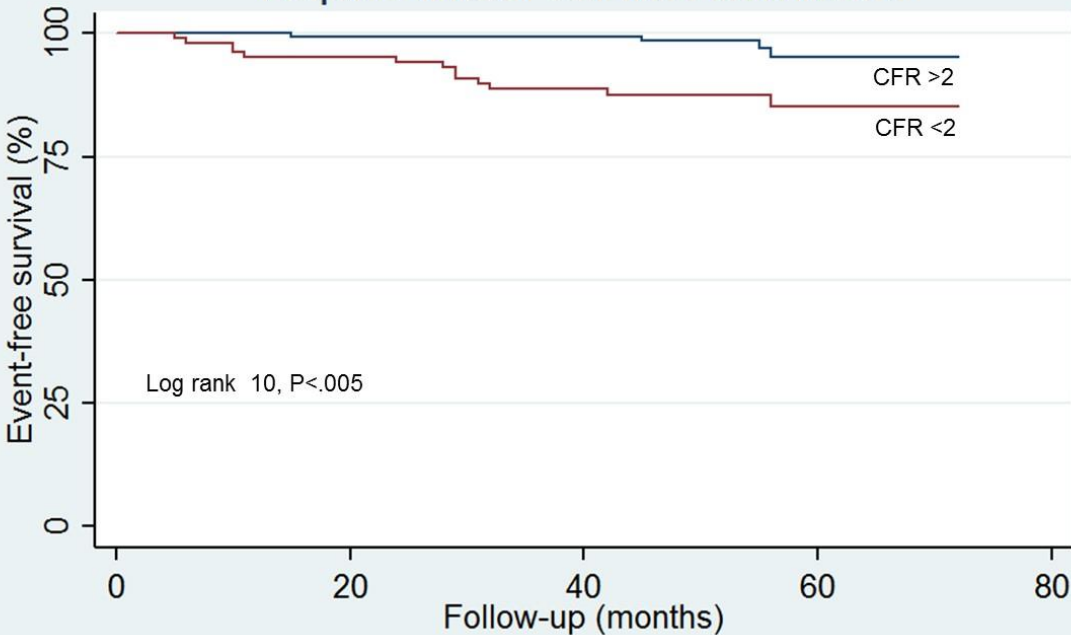
Figure 3. Incremental prognostic value (global Chi-square values on y-axis) of clinical data, CAC score and CFR

Kaplan-Meier survival estimates

Log rank 23, P<.001

Number at risk					
CAC score 0	141	127	102	53	0
CAC score 1-399	77	65	57	22	0
CAC score =400	51	44	34	13	0

Kaplan-Meier survival estimates

Number at risk

CFR >2	164	147	121	53	0
CFR <2	105	89	72	35	0