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“FEDERICO II”



SCUOLA DI MEDICINA E CHIRURGIA

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XXXV ciclo

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Tesi di Dottorato

Relationship between peri-coronary adipose tissue, coronary atherosclerotic burden and coronary vascular function by ^{82}Rb PET/CT imaging in patients with suspected coronary artery disease and normal MPI

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Summary

Aims Peri-coronary adipose tissue, [REDACTED] of coronary atherosclerosis, by releasing [REDACTED]. We evaluated the relationship between peri-coronary fat thickness (PCFT), coronary artery calcium (CAC), myocardial blood flow (MBF) and myocardial perfusion reserve (MPR), in patients with suspected [REDACTED] (CAD) and normal [REDACTED] (MPI).

Methods We studied 640 patients without overt CAD and with normal rest-stress ^{82}Rb PET/CT MPI. MPR was considered reduced when < 2 . CAC score was categorized as 0, < 400 or ≥ 400 . PCFT was calculated on CT images as the maximum fat thickness (mm) between heart surface and visceral epicardium surrounding the main coronary arteries. Patients were stratified for body mass index (BMI 30 kg/m^2).

Results Patients with MPR < 2 were significantly [REDACTED], had higher prevalence of hypertension, [REDACTED] and CAC ≥ 400 , and showed significantly lower [REDACTED] MBF and higher [REDACTED] values compared to those with normal MPR (all $p < 0.001$). Hyperemic MBF, MPR and PCFT values were [REDACTED] [REDACTED] of CAC (all p for trend < 0.001). In patients with [REDACTED] 0 and with [REDACTED] [REDACTED], those with reduced MPR had [REDACTED] PCFT values than those with normal MPR ($p < 0.001$ and $p 0.004$, respectively).

Conclusion In patients with suspected CAD and normal stress MPI, [REDACTED] and coronary [REDACTED] burden are related to blunted hyperemic MBF and MPR. In patients with low [REDACTED] PCFT was [REDACTED] in patients with [REDACTED] MPR. PCFT could help [REDACTED] vascular dysfunction.

Introduction

Adipose tissue is [REDACTED] and visceral, and fat [REDACTED] plays an important role in developing [REDACTED] (CAD) [1]. [REDACTED] obesity appears to be [REDACTED] cardiovascular risk. Accordingly, some [REDACTED] depots are [REDACTED] to contribute [REDACTED] disease while other [REDACTED] related to blood [REDACTED], heart and [REDACTED] are hypothesized to have [REDACTED] effects [2]. The [REDACTED] (EAT), a fat store [REDACTED] and myocardium, is [REDACTED] a [REDACTED] of unhealthy [REDACTED] and has been used [REDACTED] stratification [3]. One part of epicardial fat, the peri-coronary adipose tissue (PCAT), has shown to have [REDACTED] characteristics [REDACTED] with the coronary [REDACTED] in a [REDACTED] way, and may [REDACTED] vessel wall [REDACTED] [4]. Body mass index (BMI), an indicator of [REDACTED] adiposity, has been demonstrated [REDACTED] [5, 6], therefore the amount [REDACTED] may [REDACTED] according to [REDACTED] [REDACTED] and could have a different [REDACTED] [REDACTED] in [REDACTED] patients. Coronary arterial calcification (CAC) is a well-validated [REDACTED] of [REDACTED] [7], and is also considered a [REDACTED] proliferative and [REDACTED] processes into the [REDACTED] wall. Myocardial perfusion reserve (MPR) [REDACTED] vascular

function is [redacted] in the [redacted] of patients with increased [redacted] of cardiovascular [redacted], also in [redacted] with [redacted] score [8-11]. Among [redacted] imaging [redacted], rubium-82 (^{82}Rb) positron emission tomography (PET) [redacted] precise [redacted] of [redacted] and resting [redacted] (MBF) and [redacted] [12] and computed tomography (CT), due to [redacted] spatial [redacted], [redacted] the quantification of the [redacted] and [redacted] tissue [redacted]. Previous studies have [redacted] the [redacted] between peri-coronary adipose thickness (PCFT) and the [redacted] and [redacted] of atherosclerosis [13]. Moreover, the relationship [redacted] EAT [redacted] and [redacted] [14] or between [redacted] volume and both [redacted] and [redacted] function [15]. However, integration of [redacted] variables [redacted] and [redacted] parameters in patients without [redacted] CAD has [redacted] been investigated. The aim of this study was to [redacted] the relationship of PCFT, CAC score and [redacted] parameters, in patients with suspected CAD and normal myocardial perfusion imaging (MPI).

Methods

Patients

The cohort study included [REDACTED] consecutive patients undergoing stress-rest ^{82}Rb PET/CT as part of their diagnostic work-up. For the purpose of the present investigation, [REDACTED] patients with known CAD and 93 with [REDACTED] myocardial perfusion imaging were [REDACTED]. Final population included [REDACTED] patients with normal MPI. For each patient the presence of coronary risk factors was noted. Arterial hypertension was defined as repeated blood pressure (BP) measurements of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic and/or intake of antihypertensive medications [16]. Diabetes was defined when the patients had any one of the criteria as follows: fasting blood glucose ≥ 126 mg/dL, random blood glucose ≥ 200 mg/dL, blood glucose ≥ 200 mg/dL 2 h after a 75 g oral glucose tolerance test within the past 3 months, currently taking drugs to treat hyperglycemia, or prior medical diagnosis of diabetes. Hypercholesterolemia was defined as total cholesterol level > 6.2 mmol/L or treatment with cholesterol lowering medication. 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. Based on body mass index (BMI), patients were categorized as obese (≥ 30 kg/m²) or non-obese (< 30 kg/m²). Patients were defined as

symptomatic if they reported atypical angina and/or shortness of breath. This study complies with the declaration of Helsinki.

PET/CT imaging

As a routine preparation for ^{82}Rb cardiac PET/CT, patients were [REDACTED] to [REDACTED] taking nitrates for 6 h, calcium channel blockers and methylxanthine containing foods or beverages for 24 hours, and beta-blockers for 48 h 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 was performed to check patient position and low-dose CT (0.4 mSv; 120 kVp; effective tube current, 26 mA [11-mAs quality reference]; 3.3 seconds) was performed for attenuation correction, during normal breathing before and after PET acquisitions. For both rest and stress images 1110 MBq of ^{82}Rb was injected intravenously with a 7-minute list-mode PET acquisition. Dynamic PET acquisition was started at rest followed by adenosine pharmacologic stress (140 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for 4.5 minutes, with tracer administration between 2 and 2.5 minutes). Rest and stress dynamic images were reconstructed into 26-time frames (12 \times 5 seconds, 6 \times 10 seconds, 4 \times 20 seconds, and 4 \times 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. In addition, the images

were corrected for attenuation using the low-dose CT. The heart rate, systemic BP, and 12-lead ECG were recorded at baseline and throughout the infusion of adenosine. External cardiac work was estimated as rate-pressure product and was calculated as heart rate \times systolic arterial BP. Myocardial perfusion scores were calculated using an automated software (QPS, Cedars-Sinai Medical Center, Los Angeles, CA, USA). Regional myocardial perfusion was evaluated using standardized segmentation of 17 myocardial regions [17]. 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. The same procedure was applied to the resting images to calculate the summed rest score. The summed difference score was defined as the difference between the stress and rest scores. Myocardial perfusion was considered abnormal when the summed stress score was ≥ 3 . Absolute MBF (in $\text{mL} \times \text{min}^{-1} \times \text{g}^{-1}$) was computed from the dynamic rest and stress imaging series with commercially available software (Siemens Syngo Dynamic PET) [18]. MPR was defined as the ratio of hyperemic to baseline MBF and was considered reduced when < 2 [19]. The MPR values were calculated using baseline MBF corrected for rate-pressure product.

Coronary calcification was defined as a plaque with an area of 1.03 mm^2 and a density ≥ 130 HU. CAC scores were calculated according to the method described by Agatston et al. [20]. Experienced nuclear medicine physicians

analyzed the CT studies, blinded to the PET results (Syngo Multimodality Workplace; Siemens). CAC scores were calculated separately for the left anterior descending, left circumflex, and right coronary arteries and summed to provide a total CAC score. The CAC score was categorized as 0, < 400 or ≥ 400 . PCFT was calculated on axial views of CT scans as the maximum fat thickness (mm) between the surface of the heart and the visceral epicardium surrounding the three coronary arteries and the mean value was used for analyses, according to the method described by Gorter et al. [21].

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation and categorical data as percentages. A student two-sample t test and χ^2 test were used to compare the differences in continuous and categorical variables, respectively. A p value < 0.05 (two-sided) was considered significant. Univariable and multivariable linear regression analyses were performed to evaluate the relationship among coronary vascular function parameters and cardiac risk factors, PCFT and CAC score categories. Only variables showing a p value < 0.05 at univariable analysis were considered for multivariable analysis. Differences in MBF, MPR, and PCFT across levels of age and CAC score categories were assessed using one-way ANOVA. Paired post hoc comparisons were performed with Bonferroni

correction. All the analyses were performed using STATA version 14.0 for Windows (StataCorp LP, College Station, TX).

Results

Clinical characteristic and imaging findings according to MPR

Clinical characteristics and imaging findings of the [REDACTED] patients are reported in Table 1. MPR was [REDACTED] in [REDACTED] (20%) patients and [REDACTED] in [REDACTED] (80%). Patients with MPR < 2 were [REDACTED] and showed higher [REDACTED] of [REDACTED] and diabetes. Moreover, in patients with MPR [REDACTED] with those with [REDACTED] MPR, hyperemic MBF was [REDACTED] and CAC score was [REDACTED]. Patients with MPR < 2 had [REDACTED] [REDACTED] of PCFT [REDACTED] to patients with [REDACTED] MPR (Figure 1). Weak but significant [REDACTED] [REDACTED] were [REDACTED] between PCFT and MPR and [REDACTED] PCFT and [REDACTED] ($r = -0.21, p < 0.001$ and $r = -0.18, p < 0.001$, respectively).

Predictors of coronary vascular function

Linear regression analysis using MPR as dependent variable is shown in Table 2. In the univariable analysis age ($p < 0.001$), [REDACTED] ($p < 0.001$), diabetes ($p < 0.001$), hypercholesterolemia ($p = 0.04$), [REDACTED] ($p < 0.001$), and [REDACTED] ($p < 0.001$) were significant predictors of reduced MPR. In the multivariable analysis [REDACTED] ($p < 0.001$), hypertension ($p = 0.02$), diabetes ($p < 0.001$), [REDACTED] ($p = 0.02$), and [REDACTED] ($p = 0.006$) were independent predictors of reduced MPR. Linear regression analysis using hyperemic MBF as

dependent variable is shown in Table 3. In the univariable analysis age ($p < 0.001$), hypertension ($p < 0.001$), diabetes ($p < 0.001$), family history of CAD ($p = 0.02$), [REDACTED] ($p < 0.001$), and [REDACTED] ($p < 0.001$) were significant predictors of blunted hyperemic MBF. In the multivariable analysis age ($p = 0.003$), hypertension ($p < 0.001$), diabetes ($p = 0.03$), [REDACTED] ($p = 0.004$), and [REDACTED] ($p = 0.04$) were [REDACTED] predictors of [REDACTED].

Relationship of coronary vascular function, CAC score and PCFT

CAC score was [REDACTED] in [REDACTED] ([REDACTED]%) patients, [REDACTED] in 166 (26%), and [REDACTED] in 146 ([REDACTED]%). [REDACTED], MPR and [REDACTED] were [REDACTED] to [REDACTED] of CAC in the [REDACTED] population (all p for trend < 0.001), [REDACTED] was not [REDACTED] to be [REDACTED] different between [REDACTED] groups (Table 4). Additional [REDACTED] did not [REDACTED] these relations. In both patients [REDACTED], hyperemic [REDACTED] and [REDACTED] progressively [REDACTED] with [REDACTED] CAC score values whereas [REDACTED] progressively [REDACTED] (Table 4). Patients with [REDACTED] compared to those [REDACTED] had [REDACTED] PCFT values across CAC score categories (all $p < 0.05$) whereas there were no significant differences in [REDACTED] [REDACTED] and [REDACTED] [REDACTED] of CAC content. Stratifying by [REDACTED], the [REDACTED] between [REDACTED] and MPR was not different in [REDACTED] ($r = -0.22$, $p < 0.001$) and [REDACTED] patients ($r = -0.19$, $p < 0.001$) (Figure 2). On the contrary, the [REDACTED] [REDACTED] between [REDACTED] and

hyperemic MBF was slightly [redacted] in patients with BMI [redacted] ($r = -0.21$, $p < 0.001$) compared to [redacted] with BMI [redacted] ($r = -0.16$, $p < 0.005$) (Figure 3).

In patients with CAC score 0, those with [redacted] had significantly [redacted] PCFT [redacted] than those with [redacted] [redacted] (12 ± 2.3 vs. 10.5 ± 0.2 , $p < 0.001$) (Figure 4). Among patients with CAC score [redacted], PCFT was significantly [redacted] in patients with [redacted] (12.2 ± 2.1 vs. 11 ± 2 , $p = 0.004$) compared with those [redacted] (Figure 4). In patients with CAC score [redacted], no significant [redacted] were [redacted] in [redacted] between patients with [redacted] or [redacted] MPR ($p = 0.2$).

Discussion

To our knowledge, this is the first study to [REDACTED] the [REDACTED] of [REDACTED] [REDACTED] function, PCFT and [REDACTED]. In this cohort, composed of patients with [REDACTED] MPI, [REDACTED] [REDACTED] function parameters and [REDACTED] are related to [REDACTED], evaluated by [REDACTED], and [REDACTED] [REDACTED] values are associated with [REDACTED] and [REDACTED] values. This [REDACTED] relationship was [REDACTED] after stratification by [REDACTED]. Furthermore, in the [REDACTED] of patients with [REDACTED] atherosclerotic [REDACTED] (CAC score [REDACTED]), those with [REDACTED] MPR had [REDACTED] [REDACTED] of [REDACTED] compared with patients [REDACTED] MPR. From our data it also [REDACTED] that PCFT and CAC score are [REDACTED] [REDACTED] of [REDACTED] and [REDACTED] [REDACTED]. It seems that there is a [REDACTED] between [REDACTED] fat, [REDACTED] burden, and coronary [REDACTED] which can result from [REDACTED] endothelial [REDACTED] [REDACTED] to [REDACTED].

PCAT has some [REDACTED] roles and it [REDACTED] antioxidant and [REDACTED] [REDACTED] like adiponectin, and it may [REDACTED] [REDACTED] mechanisms of the [REDACTED] wall. In [REDACTED] conditions, however, dysfunctional PCAT [REDACTED], becomes [REDACTED] and [REDACTED] the infiltration of [REDACTED] and secretes [REDACTED] cytokines, with endothelial [REDACTED] [REDACTED] impairment [22]. These processes can [REDACTED] [REDACTED] of adjacent coronary [REDACTED] and [REDACTED] the progression of [REDACTED],

plaque [redacted], and [redacted] [23]. Notably, PCAT has [redacted] biological [redacted] than EAT, for example PCAT [redacted] around the [redacted] arteries and [redacted] are influenced by [redacted] [redacted] from vascular [redacted], while EAT is [redacted] to systemic [redacted], such as [redacted] and type II [redacted] mellitus [24]. Okubo et al [25] reported that PCAT instead of [redacted] [redacted] was associated with vulnerable [redacted] [redacted], [redacted] the hypothesis of local [redacted] of PCAT on plaque [redacted]. An association between [redacted] and CAC has been already [redacted] [26], but it was also previously described that PCAT [redacted] is [redacted] surrounding coronary [redacted] with plaque and the [redacted] volume was nearby [redacted] [redacted], compared to those with [redacted], suggesting that PCAT is involved in an [redacted] and [redacted] [redacted] of atherosclerosis, than [redacted] and [redacted] phase of disease, in which [redacted] are [redacted] [27].

The [redacted] and [redacted] of calcification, [redacted] by CT, [redacted] the atherosclerotic [redacted] in the coronary arteries and can be [redacted]. A score of 0 [redacted] no coronary [redacted] and predicts [redacted] risk, and a score [redacted] reflects the presence of calcification from [redacted] to [redacted] and higher risk of [redacted] cardiovascular [redacted] [28]. The integration of CAC score can [redacted] [redacted] diagnostic [redacted] [29] and could [redacted] the cardiac risk [redacted] [9,30]. Some studies have [redacted] the relationship of CAC

score and coronary vascular function [31,32] and a [REDACTED] increase in the [REDACTED] of reduced MPR with increasing [REDACTED] was found. The possible explanation of this finding is that [REDACTED] incorporates [REDACTED] on diffuse epicardial disease and [REDACTED] atherosclerosis [33]. Thus, the [REDACTED] of coronary vasodilator [REDACTED], reflecting disease activity, is a [REDACTED] of vascular [REDACTED] and may promptly and better detect [REDACTED] [REDACTED] than coronary [REDACTED], also in response to [REDACTED]. A [REDACTED] point is that [REDACTED] can improve [REDACTED] irrespective of [REDACTED] of CAC in patients with [REDACTED] CAD and other [REDACTED] [9-11,32,34]. We found that in patients with [REDACTED], PCFT values were [REDACTED] with [REDACTED] MPR. This [REDACTED] that patients [REDACTED] identified as [REDACTED] could [REDACTED] coronary vascular [REDACTED]. Additional research is needed to [REDACTED] whether the integration of [REDACTED] and [REDACTED] data could [REDACTED] patients at [REDACTED] risk of cardiac [REDACTED] and [REDACTED] from more [REDACTED] efforts of [REDACTED].

This study has some limitations. This is a single-center retrospective study in a cohort of patients with [REDACTED] and angiographic data were not [REDACTED]. Therefore, a possible [REDACTED] of coronary [REDACTED] on [REDACTED] MPR cannot be excluded. Moreover, we did not evaluate PCAT [REDACTED] and [REDACTED],

that require more [REDACTED] processing [REDACTED], however high [REDACTED] [REDACTED] could be considered expression of high [REDACTED] and so of [REDACTED] [REDACTED]. Finally, waist [REDACTED] was not assessed, so we did not [REDACTED] the relationship of PCFT and [REDACTED] [REDACTED], but we used a BMI [REDACTED] as an [REDACTED] of metabolic [REDACTED].

Conclusion

In patients with [REDACTED] and normal stress MPI, [REDACTED] PCFT [REDACTED] and coronary [REDACTED] [REDACTED] are related to [REDACTED].

In patients with [REDACTED], PCFT was [REDACTED] in patients with [REDACTED] MPR. PCFT could [REDACTED] to [REDACTED] patients at [REDACTED] of coronary vascular [REDACTED].

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Table 1 Clinical characteristics and imaging findings of patients according to MPR

	All patients (<i>n</i> = 640)	MPR < 2 (<i>n</i> = 130)	MPR > 2 (<i>n</i> = 510)	<i>p</i> value
Age (years)	60 ± 13	64 ± 13	59 ± 13	< 0.001
Male gender	307 (48)	62 (48)	245 (48)	1.00
BMI (kg/m ²)	30.6 ± 6.7	30.5 ± 7	30.7 ± 6.7	0.82
BMI ≥ 30 kg/m ²	313 (49)	63 (48)	250 (49)	0.91
Hypertension	505 (79)	121 (93)	384 (75)	< 0.001
Diabetes	170 (27)	61 (47)	109 (21)	< 0.001
Hypercholesterolemia	462 (72)	101 (78)	361 (71)	0.13
Smoking history	205 (32)	41 (31)	164 (32)	0.92
Family history of CAD	286 (45)	54 (41)	232 (45)	0.43
Symptoms	465 (73)	81 (62)	384 (75)	< 0.005
Baseline MBF (mL/min/g)	1.07 ± 0.25	1.09 ± 0.2	1.06 ± 0.26	0.09
Hyperemic MBF (mL/min/g)	2.7 ± 0.78	1.97 ± 0.65	2.89 ± 0.7	< 0.001
PCFT (mm)	11 ± 2	12.1 ± 2.2	10.9 ± 1.9	< 0.001
CAC score categories				< 0.001
0	328 (51)	43 (33)	285 (56)	
< 400	166 (26)	35 (27)	131 (26)	
≥ 400	146 (23)	52 (40)	94 (18)	

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

BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; PCFT, peri-coronary fat thickness.

Table 2 Linear regression analysis with MPR as dependent variable

	Univariable analysis			Multivariable analysis		
	β coefficient	SE	<i>p</i> value	β coefficient	SE	<i>p</i> value
Age	-0.276	0.002	< 0.001	-0.203	0.002	< 0.001
Male gender	0.071	0.063	0.07			
BMI	0.006	0.004	0.88			
Hypertension	-0.172	0.072	< 0.001	-0.087	0.072	0.02
Diabetes	-0.188	0.067	< 0.001	-0.15	0.066	< 0.001
Hypercholesterolemia	-0.081	0.067	0.04	0.043	0.066	0.28
Smoking history	-0.006	0.064	0.89			
Family history of CAD	0.059	0.06	0.14			
CAC score \geq 400	-0.207	0.07	< 0.001	-0.095	0.071	0.02
PCFT	-0.207	0.014	< 0.001	-0.107	0.014	0.006

BMI, body mass index; CAD, coronary artery disease; CAC, coronary artery calcium; MPR, myocardial perfusion reserve; PCFT, peri-coronary fat thickness.

Table 3 Linear regression analysis with hyperemic MBF as dependent variable

	Univariable analysis			Multivariable analysis		
	β coefficient	SE	<i>p</i> value	β coefficient	SE	<i>p</i> value
Age	-0.219	0.002	< 0.001	-0.121	0.002	0.003
Male gender	-0.077	0.062	0.06			
BMI	0.025	0.005	0.53			
Hypertension	-0.215	0.074	< 0.001	-0.088	0.072	< 0.001
Diabetes	-0.135	0.069	< 0.001	-0.085	0.067	0.03
Hypercholesterolemia	-0.103	0.067	0.13			
Smoking history	-0.039	0.066	0.33			
Family history of CAD	0.089	0.062	0.02	0.046	0.059	0.22
CAC score \geq 400	-0.206	0.07	< 0.001	-0.117	0.075	0.004
PCFT	-0.176	0.015	< 0.001	-0.08	0.015	0.04

BMI, body mass index; CAD, coronary artery disease; CAC, coronary artery calcium; MBF, myocardial blood flow; PCFT, peri-coronary fat thickness.

Table 4 MPR, MBF and PCFT in relation to CAC score in all patients and in subpopulations stratified by body mass index

	CAC			<i>p</i> value for trend
	0	< 400	≥ 400	
All patients (<i>n</i> = 640)	328 (51%)	166 (26%)	146 (23%)	
Baseline MBF (mL/min/g)	1.08 ± 0.28	1.05 ± 0.26	1.07 ± 0.29	0.35
Hyperemic MBF (mL/min/g)	2.88 ± 0.79	2.6 ± 0.7	2.41 ± 0.72	< 0.001
MPR	2.74 ± 0.75	2.54 ± 0.74	2.3 ± 0.68	< 0.001
PCFT (mm)	10.7 ± 2	11.27 ± 2	12 ± 1.89	< 0.001
Patients stratified by BMI				
BMI < 30 kg/m ² (<i>n</i> = 327)	149 (45%)	94 (29%)	84 (26%)	
Baseline MBF (mL/min/g)	1.07 ± 0.28	1.04 ± 0.26	1.06 ± 0.28	0.47
Hyperemic MBF (mL/min/g)	2.95 ± 0.75	2.57 ± 0.7	2.35 ± 0.79	< 0.001
MPR	2.87 ± 0.78	2.53 ± 0.72	2.23 ± 0.7	< 0.001
PCFT (mm)	10.07 ± 1.79	10.93 ± 1.92	11.49 ± 1.67	< 0.001
BMI ≥ 30 kg/m ² (<i>n</i> = 313)	179 (57%)	72 (23%)	62 (20%)	
Baseline MBF (mL/min/g)	1.09 ± 0.28	1.05 ± 0.25	1.09 ± 0.31	0.78
Hyperemic MBF (mL/min/g)	2.84 ± 0.83	2.64 ± 0.72	2.49 ± 0.63	0.006
MPR	2.64 ± 0.72	2.54 ± 0.78	2.39 ± 0.6	0.06
PCFT (mm)	11.23 ± 2.07	11.73 ± 2.13	12.55 ± 2.02	< 0.001

BMI, body mass index; CAC, coronary artery calcium; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; PCFT, peri-coronary fat thickness

Figure Legends

Figure 1 Peri-coronary fat [REDACTED] in patients with [REDACTED] and [REDACTED] myocardial perfusion reserve. Patients with [REDACTED] myocardial perfusion reserve have [REDACTED] peri-coronary fat thickness values ($p < 0.001$)

Figure 2 [REDACTED] between peri-coronary fat [REDACTED] and myocardial perfusion reserve estimated by [REDACTED] analysis in patients with [REDACTED] [REDACTED] (red) and [REDACTED] (blue)

Figure 3 [REDACTED] between peri-coronary fat [REDACTED] and hyperemic [REDACTED] blood flow estimated by [REDACTED] analysis in patients with [REDACTED] (red) and [REDACTED] (blue)

Figure 4 [REDACTED] in peri-coronary fat thickness values according to [REDACTED] status and [REDACTED] groups (A, B, and C). In patients with CAC score [REDACTED], those with [REDACTED] myocardial perfusion reserve have significantly [REDACTED] peri-coronary fat thickness values







