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Human coronary inflammation by computed tomography: Relationship with coronary microvascular dysfunction

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ABSTRACT

Background A new imaging metric using coronary computed tomography angiography (CCTA), addressing the peri-coronary adipose tissue (PCAT) computed tomography (CT) attenuation, has been clinically validated. This method provides information regarding coronary inflammation. It is unclear how coronary inflammation affects microvascular function. The non-invasive evaluation of coronary flow velocity reserve is widely used in clinical practice using Doppler measurement on the left anterior descending coronary artery (CFVR-lad) during stress-echocardiography (SE). We hypothesize that coronary inflammation affects CFVR-lad and, in the absence of overt CAD, they are significantly correlated.

Methods We evaluated the relationship between coronary inflammation (by PCAT CT attenuation) and coronary microvascular function (by CFVR-lad) in subjects with no or non-obstructive (diameter stenosis <70%) coronary artery disease (CAD).

Results Two-hundred and two subjects were enrolled in the study. The relationship between PCAT CT attenuation and CFVR-lad show a significant inverse relationship in the entire group of subjects enrolled in the study ($r = -0.32$, $p < 0.001$). Correlation between PCAT CT attenuation and CFVR-lad was significant in subjects with no or mild CAD-lad, while this was not the case in subjects with intermediate CAD-lad. The R and R^2 were respectively −0.40, −0.16 in subjects without CAD ($p < 0.001$) and − 0.35 and − 0.12 in subjects with mild CAD-lad ($p = 0.001$).

Conclusions The main finding of the current study is the independent relationship between coronary microvascular function, by Doppler CFVR-lad during SE, in subjects without severely obstructive CAD in the left anterior descending coronary artery, and the level of local coronary inflammation, by PCAT attenuation measurement on CCTA.

1. Introduction

Vascular inflammation is a key feature of atherogenesis [1,2]. A healthy endothelium mediates endothelium-dependent vasodilation and suppresses low-grade inflammation, which is typical of early stage atherosclerosis and influences the progression of atherosclerotic plaques [2–4].

Vascular inflammation is not detectable by common imaging techniques, and the measurement of circulating inflammatory molecules cannot differentiate dysfunctional arteries (or vulnerable plaques) from the others; a new imaging metric using coronary computed tomography angiography (CCTA), addressing peri-coronary adipose tissue (PCAT) computed tomography (CT) attenuation, has been clinically validated [5,6]. This method provides information regarding coronary inflammation and can potentially track its variations [7], since in presence of vascular inflammation adipogenesis is inhibited in favor of lipolysis and water content increases in the adipose cells [5]. This process shifts overall PCAT CT attenuation toward the aqueous

Abbreviations: CCTA, coronary computed tomography angiography; PCAT, peri-coronary adipose tissue; CT, computed tomography; CFVR-lad, coronary flow velocity reserve on the left anterior descending coronary artery; SE, stress echocardiography; CAD, coronary artery disease; PCAT-lad, peri-coronary adipose tissue on the left anterior descending artery; PCAT-rca, peri-coronary adipose tissue on the right coronary artery; LVEF, left ventricle ejection fraction; LAD, left anterior descending coronary artery; HU, Hounsfield Units.

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phase (less negative Hounsfield Units, HU) and makes such attenuation measurement a useful biomarker for the in-vivo assessment of coronary inflammation [5–9]. PCAT CT attenuation is incremental to clinical risk factors and the presence and type of coronary plaques in the prediction of future cardiovascular events; however, it is still unclear how coronary inflammation affects microvascular function [9].

The non-invasive evaluation of coronary flow velocity reserve entered the clinical practice with the feasibility of Doppler measurement on the left anterior descending coronary artery (CFVR-lad) during stress-echocardiography (SE) [10]. Reduced CFVR-lad associates with higher cardiac (and non-cardiac) mortality regardless of the presence of flow-limiting epicardial coronary artery disease (CAD) [11–13]. We hypothesize that coronary inflammation may functionally affect CFVR-lad and hence, in the absence of overt CAD, they should be significantly correlated. We designed the current study to evaluate the relationship between coronary inflammation (measured by PCAT CT attenuation) and coronary microvascular function (measured by CFVR-lad on SE) in subjects with no or mild-to-moderate obstructive CAD on the left anterior descending coronary artery. PCAT-lad was used as the vessel-specific measure of inflammation matching the site of CFVR-lad measurement, while PCAT on the right coronary artery (PCAT-rca) was the patient-level representative biomarker of coronary inflammation.

2. Patients and methods

2.1. Patients and study design

This is a cross-sectional observational single-center study, including subjects recruited from a prospectively collected 2009–2018 SE database. From the initial overall cohort of 3770 subjects who underwent pharmacological dipyridamole SE for a suspected chest pain syndrome and who had not undergone coronary artery bypass surgery or percutaneous revascularization before SE, we selected the 478 subjects who also underwent CCTA during their diagnostic work-up. Among these 478 subjects, only the 219 subjects who had both tests (SE and CCTA, either one first) performed within a short interval (<3 months) were selected. Subjects with a severe stenosis of the left anterior descending coronary artery (maximal stenosis ≥70%) and/or of the left main trunk stenosis (maximal stenosis ≥50%) at CCTA were finally excluded. The analyses were consequently performed in a final sample of 202 subjects whose CCTA profile was not having any severe (≥70% diameter) stenosis on the left anterior descending coronary artery or on the left main trunk (for the left main trunk the definition of non-severe stenosis was <50%) (see Fig. 1, available in the online appendix).

The characteristics of all patients and comorbidities were collected from clinical records at the time they performed the index tests. The presence of cardiovascular risk factors was defined as follows: diabetes mellitus, fasting plasma glucose level >125 mg/dl or treatment with antidiabetic agents; hypercholesterolemia, total cholesterol >200 mg/dl and or triglycerides >149 mg/dl or treatment with lipid-lowering drugs; hypertension, blood pressure >140/90 mmHg or use of antihypertensive drugs; obesity, body mass index ≥30 kg/m^2. The study was approved by the Institutional Review Board of the Hospitals of Venice, Serenissima Regional Health System. Eligible patients were informed about the purpose of study, and informed consent was obtained from all study participants.

2.2. Stress-echocardiography

Philips ie33 (Philips Medical Systems) was used with the standard S5 transducer(1–5 mHz). The protocol used for accelerated high-dose dipyridamole (0.84 mg/kg/6 min) SE has been described elsewhere [11,12]. Briefly, it consists in serial assessments of wall motion abnormalities at rest and during pharmacological stress. Left ventricle ejection fraction (LVEF) was measured with Simpson's biplane method. The left ventricle is divided in 17 segments according to the recommendations of the American Society of Echocardiography [14]. Segmental wall motion is graded as follows: normal = 1; hypokinetic = 2; akinetic = 3; and dyskinetic = 4. Reversible ischemia was defined as the occurrence of a stress-induced new dyssynergy or worsening of rest hypokinesia in ≥1 segment.

Spectral Doppler CFVR-lad was obtained as peak diastolic velocity stress/rest ratio, using a modified apical 3-chamber view, with small boluses of 0,3 ml microbubble ultrasound contrast (SonoVue· Bracco, Milan) if needed for signal enhancement, in conjunction with low mechanical index for color and pulse-wave Doppler imaging. Stress acquisition was performed 1 min after the end of the dipyridamole administration (0,84 mg/kg in 6 min).

2.3. Coronary Computed Tomography and coronary artery disease analysis

All coronary CCTA examinations were performed using a Dual Source CT system (Somatom Definition FLASH, Siemens Healthcare, Forchheim, Germany). The data set was analyzed by two experienced readers using an off-line workstation software package (Leonardo, Siemens Medical Solutions, Forchheim, Germany). Angiographic CT datasets of the reconstructed coronary vessels were created in the best phase of the cardiac cycle depending on the heart rate of the patient (end-diastolic cardiac phase usually set at 60% of the R-R interval or end-systolic phase set at 30% of the R-R interval). The presence of plaques was assessed using original axial images, multiplanar reconstruction, and cross-sectional reconstruction. The coronary segments were analyzed following the classification of the American Heart Association [15], and each segment was delimited by identifiable side-branches. For the final grading of stenosis severity, we used the following criteria for the left anterior descending coronary artery: 0 = no stenosis; 1 = mild stenosis (maximal diameter stenosis <50%), 2 = intermediate stenosis (50–69%), 3 = severe stenosis (70–99%).

2.4. Peri-coronary Fat CT Attenuation

To measure PCAT CT attenuation one experienced reader (NG) used a dedicated image analysis software package (Aquarius Workstation® V.4.4.13, TeraRecon Inc., Foster City, CA, USA). We traced proximal 40-mm segments of two major epicardial coronary vessels (right coronary artery 10 mm distal to the ostium, left anterior descending coronary artery starting right at the ostium) and defined peri-vascular fat as the adipose tissue within a radial distance from the outer vessel wall equal to the diameter of the vessel. We ascertained the PCAT CT attenuation by quantifying the weighted perivascular fat attenuation after adjustment for technical parameters based on the attenuation histogram of perivascular fat within the range − 190 HU to −30 HU, as described previously [6–9]. The measurement performed around the left anterior descending coronary artery was defined as PCAT-lad and around right coronary artery as PCAT-rca. (See online appendix for technical details of CCTA methods and PCAT CT attenuation measurements).

2.5. Statistical analysis

Variables normally distributed were analyzed with parametric tests, while non-normally distributed with non-parametric tests. We divided subjects into 3 subgroups according to the presence and grade of CAD in the left anterior descending coronary artery (CAD-lad) on CCTA: 1. No CAD-lad, absence of any measurable plaque or stenosis; 2. Mild CAD-lad, maximal diameter stenosis <50%; 3. Intermediate CAD-lad, stenosis 50–69%.

Correlation between two continuous variables was assessed using Pearson's correlation coefficient. Differences among groups were evaluated by the analysis of variance (ANOVA) with the Bonferroni test as post-hoc test, and the Chi-Square test. Linear regression analyses were performed to evaluate the relationship between CFVR-lad and PCAT-lad or PCAT-rca. The multivariate regression analysis was performed

Table 1
Demographics, clinical characteristics, medications data in the study population and groups divided by CAD-lad severity at CCTA.

Variables	All subjects	No CAD-lad	Mild CAD-lad	Intermediate CAD-lad	*p*-Value
Number	202	78	83	41	
Age, y, mean (±SD)	59(±11)	54(±11)	61(9)	66(±8)	<0.001
<40 years n(%)	6(3)	6(8)	0(0)	0(0)	
40–49 years n(%)	34(17)	23(30)	11(13)	0(0)	
50–59 years n(%)	59(29)	25(32)	25(30)	9(22)	<0.001
60–69 years n(%)	71(35)	17(22)	33(40)	21(51)	
≥70 years n(%)	32(16)	7(9)	14(17)	11(27)	
Female sex, n (%)	80(40)	45(58)	27(32)	8(20)	<0.001
Hypertension n (%)	117(58)	40(51)	51(61)	26 (63)	0.29
Hyperlipidemia n (%)	114(56)	35(44)	47(57)	32(78)	0.002
Current smoker n (%)	79(39)	25(32)	34(41)	20(49)	0.067
Diabetes mellitus n (%)	22(11)	5(6)	12(14)	5(12)	0.258
CAD Family History n (%)	82(41)	28(36)	42(51)	12(29)	0.055
Obesity n (%)	36(18)	16(20)	16(19)	4(10)	0.61
Peripheral arterial disease n(%)	33(16)	6(8)	13(16)	14(34)	0.001
Prior Stroke n(%)	6(3)	0(0)	1(1)	5(12)	0.002
Atrial fibrillation n (%)	15(7)	5(6)	8(10)	2(5)	0.61
Aspirin	71(35)	14(18)	32(39)	25(61)	<0.001
ACE-inhibitor/ARB	94(47)	29(37)	42(51)	23(56)	0.06
Beta-Blocker	80(40)	29(37)	32(38)	19(46)	0.41
Statin	72(36)	20(26)	30(36)	22(54)	0.01
Diuretic	36(18)	16(20)	15(18)	5(12)	0.64

CAD indicates coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCTA, coronary computed tomography angiography. Chi square test was used to compare CAD-lad groups.

to evaluate the potential independent association between CFVR-lad and PCAT-lad after adjustment for typical CAD risk factors: age, sex, hypertension, hyperlipidemia, diabetes, smoking, and obesity. All analyses were made using SPSS software, version 23.0.

3. Results

Two-hundred two subjects, 122 males and 80 females, were enrolled in the study. Characteristics of all subjects and groups of subjects divided according to the absence or presence of mild or intermediate CAD evaluated by CCTA in the left anterior descending coronary artery are displayed in Table 1. Subjects with intermediate CAD-lad compared with mild or no CAD-lad were older, had a higher prevalence of male sex, hyperlipidaemia, stroke and peripheral arterial disease. A higher number of subjects in the intermediate grade CAD-lad (the most severe grade of CAD included in this study) were more often taking aspirin and statins, as expected. As shown in Table 2 (available in the online appendix), no significant differences in baseline LVEF or fixed or inducible wall motion abnormalities during SE were detected among CAD-lad subgroups. CFVR-lad was instead significantly lower in subjects with intermediate left anterior descending coronary artery stenosis compared to subjects without CAD-lad or with mild CAD-lad. PCAT-lad was comparable among subgroups: PCAT-lad was −66.4 ± 9.3 HU in the no CAD-lad group, −67.8 ± 10.8 HU in mild CAD-lad group, −66.6 ± 9.2 HU in intermediate CAD-lad group ($p = 0.61$). Agatston score, as expected, was significantly higher in the group with more significant CAD. Agatston score was not correlated with PCAT-lad (Spearman's rho = 0.0001, $p = 0.492$).

PCAT-lad values among the groups of subjects divided by CFVR-lad quartiles are reported in Fig. 1 (left), showing a statistically significant difference among CFVR-lad groups (One way ANOVA $p < 0.001$). The relationship between PCAT-lad and CFVR-lad in all subjects is also reported in Fig. 1 (right), showing a significant, although mild-to-moderate inverse relationship between the two variables in the entire group of subjects enrolled in the study ($r = -0.32$, $p < 0.001$).

Fig. 3 (available in the online appendix) shows the same simple linear correlation analysis, but in this case in subjects divided according to the grade of CAD-lad. Correlation between PCAT CT attenuation and CFVR-lad was significant in subjects with no or mild CAD-lad (Fig. 3a and b), while this was not the case in subjects with intermediate CAD-lad (Fig. 3c). Specifically, the R and R^2 were respectively −0.40, −0.16 in subjects without CAD ($p < 0.001$) and − 0.35 and − 0.12 in subjects with mild CAD-lad ($p = 0.001$). We also tested the single components of CFVR-lad (rest and stress Doppler velocity) versus PCAT-lad, and we found that only stress left anterior descending coronary artery velocity was significantly correlated with PCAT-lad ($r = -0.26$, $p = 0.002$), while rest velocity was not ($r = 0.08$, $p = 0.31$) (see figure in the online appendix). Finally, we tested whether CFVR-lad was associated also with PCAT-rca, but no significant relationship was found in this case ($r = 0.129$, $r^2 = 0.017$, $p = 0.068$).

Fig. 2 shows the PCAT-lad values in the subgroups of subjects either with no CAD (Fig. 2A) or mild to intermediate ("non-obstructive") CAD

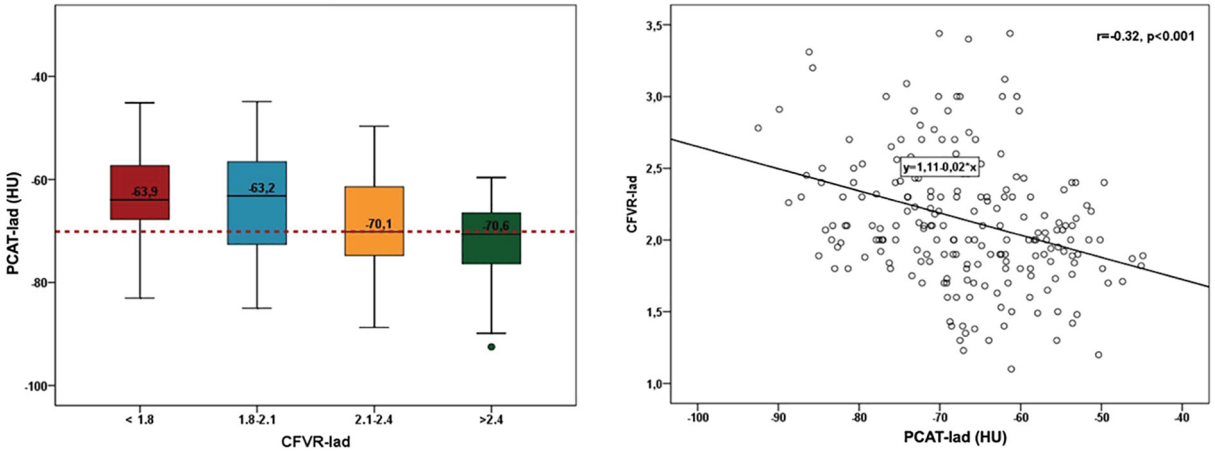

Fig. 1. PCAT-lad values among the overall study population divided by CFVR-lad quartiles (left) and PCAT-lad vs. CFVR-lad relationship in the study population (right). A statistically significant difference among CFVR-lad groups was observed ($p = 0.000$, Welch's one-way ANOVA). Games-Howell post-hoc test: <1.8 vs 1.8–2.1 = ns; <1.8 vs 2.1–2.4 *; <1.8 vs >2.4 ***; 1.8–2.1 vs >2.4*.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Dotted line cut-off = −70.1 HU.
PCAT-lad, peri-coronary adipose tissue attenuation on the left anterior descending coronary artery; CFVR-lad, coronary flow velocity reserve on the left anterior descending coronary artery.

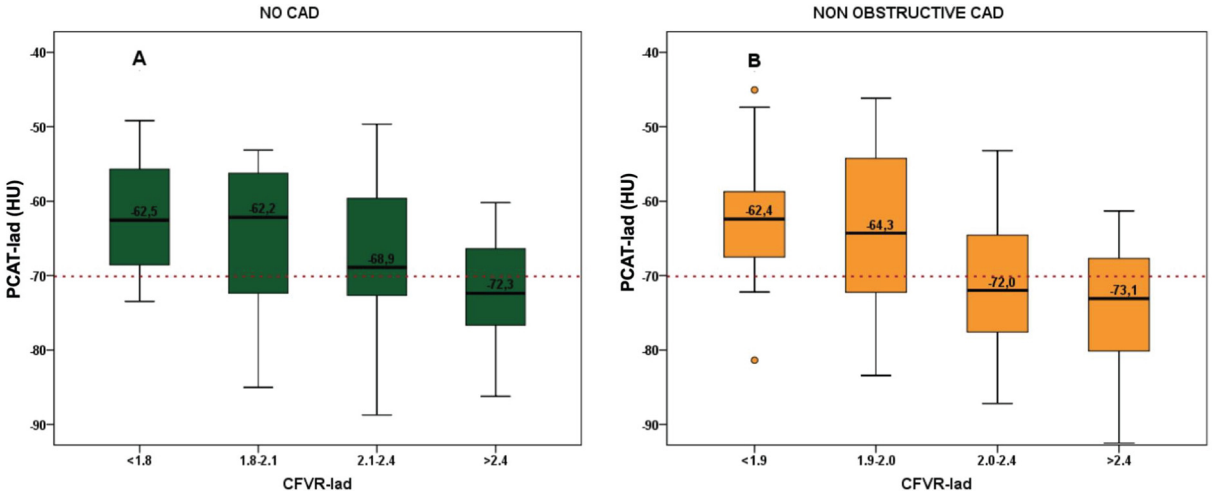

Fig. 2. PCAT CT attenuation values distribution among subgroups population divided by CFVR-lad quartiles and separated according to severity of overall CAD, either with no CAD (A) or mild to intermediate ("non-obstructive") CAD (B) and divided by CFVR-lad quartiles.
A. A statistically significant difference across CFVR-lad quartiles in no CAD subgroup was observed (one-way ANOVA, $p = 0.01$). The only significant difference is between two quartiles: <1.8 and >2.4 **, all other comparisons are not significant. See Fig. 3 for abbreviations.
B. A statistically significant difference across CFVR-lad quartiles in non-obstructive CAD subgroup was observed (one-way ANOVA, $p = 0.001$). The only significant difference between quartiles are: 1) <1.9 vs 2.0–2.4 *; 2) <1.9 vs >2.4 **; 3) 1.9–2.0 vs >2.4* (Bonferroni post-hoc test).

(Fig. 2B) divided by CFVR-lad quartiles; in both groups PCAT-lad was significantly different among the subgroups (one-way ANOVA, $p = 0.001$ and $p = 0.001$, respectively). To further investigate the independent relationship between PCAT-lad and CFVR-lad, a multivariable regression analysis was performed including age, sex, hypertension, hyperlipidemia, diabetes, smoking, and obesity as additional independent variables. PCAT-lad was independently and inversely associated with CFVR-lad; age, hypertension, and obesity were also independently associated with CFVR-lad, as shown in Table 2.

4. Discussion

The main finding of the current study is the independent relationship found between coronary flow reserve, assessed with Doppler CFVR-lad during SE, and the level of local coronary inflammation, assessed on CCTA using PCAT CT attenuation measurement in subjects enrolled based on the absence of severely obstructive CAD (defined as maximal diameter stenosis ≥70%) on the left anterior coronary artery.

The correlation between PCAT CT attenuation and coronary flow reserve was significant only in in the subgroup of patients with no or less than 50% maximal diameter coronary stenosis, which is the clinical setting in which CFVR-lad is mostly determined by microvascular function.

The current findings suggest that inflammation and microvascular dysfunction coexist in the early phases of atherosclerosis, while this association may be confounded in presence of advanced and obstructive CAD. This finding seems to be indirectly confirmed by the seminal study first reporting on the prognostic value of PCAT CT attenuation, in which the presence of inflamed coronary arteries (PCAT CT attenuation < −70.1 HU) was less predictive of negative outcomes in the subgroup with severe/obstructive CAD, compared with the subgroup with non-obstructive CAD [6].

Table 2
Results of multiple regression analysis with CFVR-lad as the outcome variable.

Variables	B (95% CI)	Standardized β	*p* Value
Constant	1.71 (1.19–2.24)		
PCAT-lad	−0.016 (−0.022, −0.009)	−0.321	<0.001
Male sex	0.028 (−0.097, 0.152)	0.028	0.66
Hypertension	−0.201 (−0.332, −0.069)	−0.207	0.003
Age groups	−0.009 (−0.015, −0.003)	−0.202	0.004
Obesity	0.184 (0.022, 0.346)	0.149	0.027
Dyslipidemia	0.008 (−0.115, 0.131)	0.008	0.897
Cigarettes smoke	−0.035 (−0.161, 0.091)	−0.036	0.588
Diabetes	0.049 (−0.147, 0.246)	0.032	0.621

Constant variable in the table represents a patient with no risk factors, and the beta-coefficients represent a reduction in the CFVR-lad for each risk factor or Hounsfield unit of PCAT-lad added.

The absence of correlation between CFVR-lad and PCAT-lad in patients with obstructive CAD should be cautiously interpreted as far as microcirculatory function is concerned, since it could be due to the inherent limitation of CFVR measurement being less reliable as a measure of microcirculatory function in presence of flow-limiting epicardial stenosis, which reduces CFVR independently from the degree of microvascular dysfunction.

CFVR has been correlated with several cardiovascular diseases, and is one of the most robust predictors of death, both cardiovascular and (at least according to some studies) also non-cardiovascular in nature [11–13,16,17]. Coronary inflammation has been suggested as a plausible pathophysiological atherogenic mechanism and, although direct data in humans are scant [18,19], at least three studies, the CANTOS [20], the COLCOT [21] and the recent LoDoCo2 [22] have indirectly demonstrated this link, since long-term anti-inflammatory treatments effectively reduced the risk of cardiovascular events, most probably by reducing inflammation. Such prospective studies reinforced the concept of inflammation as a clinical marker to evaluate the residual cardiovascular risk of a subject and we may speculate anti-inflammatory drugs would have been even more successful, had the investigators selected patients based on a local coronary inflammation measurement, rather than systemic inflammation markers. The role of PCAT CT attenuation as a predictor of cardiovascular events has been robustly demonstrated [6,9,23–25] and it is now considered a promising prognostic tool to identify the residual inflammatory risk beyond classic cardiovascular risk factors. We speculate that the measurement of PCAT CT attenuation might also be useful to identify subjects with (or more at risk of) isolated or predominant microvascular dysfunction in the absence of obstructive CAD.

Other variables in our sample associated with CFVR-lad were age and hypertension. This result is concordant with other studies. We have also found an interesting positive correlation between obesity and CFVR. A previous study has shown an inverse independent J-shaped relationship between BMI and CFVR, such that in obese patients, CFVR decreased linearly with increasing BMI, although

subjects with class I obesity had similar CFVR values compared to normal weight subjects [26]. In our study population, the obese subgroups had BMI values of class I mild obesity: this could partially explain our findings.

No significant relationship between CFVR-lad and PCAT-rca was found in our study, suggesting a key role of local rather than generalized coronary inflammation status on microvascular dysfunction.

4.1. Comparison with previous studies

Only one prior study addressed the relation between coronary flow reserve and inflammation measured by PCAT CT attenuation. The investigators used positron emission tomography (PET) to measure coronary blood flow reserve and the study suggested that impaired coronary flow reserve and PCAT CT attenuation are significantly correlated [27]. This well-conducted study has the merit to assess coronary flow reserve in all the three coronary arteries, thanks to the absence of the technical limitations of ultrasound limiting the feasibility of reliable CFVR measurement to the left anterior descending coronary artery; the study was performed in fewer patients, and specifically in only 68 patients with no CAD or <50% diameter stenosis CAD, while in our study we selected mostly patients (161 out of 202 overall, 80%) without CAD or with <50% CAD, so that we could focus more specifically on the assessment of microvascular function thanks to the removal of the confounding effect of obstructive CAD. The findings of our study, obtained using a different method (Doppler ultrasound) for the assessment of coronary flow reserve, are concordant with the abovementioned PET study and reinforce such findings in concluding that PCAT CT attenuation is inversely associated with coronary flow reserve.

4.2. Inflammation and microcirculation

The human microcirculation plays a critical role in tissue perfusion and is recognized as a modulator of the local tissue environment, crucial for initiation and progression of several chronic, life-threatening diseases [28]. Microcirculatory dysfunction is associated with chronic inflammation, so that the microcirculatory function may also partially mirror the inflammatory status of the patient [29–31].

Systemic inflammation is related to coronary microvascular dysfunction, measured as an abnormal CFVR which shows an inverse correlation with the concentration of inflammatory circulating cytokines (such as tumor necrosis factor-alpha and interleukin-6) in patients with normal epicardial coronary arteries or with inflammatory autoimmune conditions, which have also been linked to an increased cardiovascular risk [32].

The mechanism underlying the development of abnormal vasomotion can be the result of a mutually depending interaction of inflammation with oxidative stress. Enhanced reactive oxygen species formation within coronary arterioles can functionally impair vascular function, by reducing production and/or availability of NO and, hence, leading to the impairment of the endothelium-dependent and endothelium-independent NO-mediated vasodilation [33,34]. In our study only the reduced coronary flow velocity at stress was significantly associated with PCAT-lad, suggesting the dipyridamole-induced vasodilation is the component affected by inflammation.

The role of inflammation as a trigger or as a co-trigger in the development of microvascular dysfunction is intriguing. Prospective studies are needed to confirm this hypothesis, but PCAT CT attenuation may now be considered an appropriate non-invasive tool for this type of local coronary inflammation assessment.

4.3. Study limitations

This study has also some limitations. CCTA and SE were not necessarily performed in a given order and the requirement of a less than 3-month interval between CCTA and SE can be not negligible considering the dynamic nature of coronary inflammation; the median interval between the two tests was anyway 38 days, which is probably reasonable to minimize time-related variations. All limitations of the studies with a retrospective design also apply to the current study: in particular, a causative role of inflammation over microvascular dysfunction, or reverse, cannot be established, since they could both represent downstream markers of another unknown primary process, due to the inherent limitations of the retrospective and observational design of the current study.

5. Conclusions

Our study shows a direct relationship between coronary inflammation measured with PCAT CT attenuation on CCTA and coronary microvascular dysfunction measured with Doppler CFVR during SE, in particular in patients without obstructive CAD. The detection of coronary inflammation on CCTA may represent a useful marker to detect early coronary blood flow reserve abnormalities and to recognize subjects who may require more intensive preventive treatment, before CAD fully develops.

Conflicts of interest

Nothing to Disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.05.040.

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