© Pol J Radiol 2023; 88: e141-e148
DOI: https://doi.org/10.5114/pjr.2023.126084

Received: 26.08.2022
Accepted: 12.12.2022
Published: 18.03.2023

Polish Journal of Radiology

http://www.polradiol.com

Original paper

Determinants of perivascular adipose tissue stranding as a novel imaging marker and its relation to inflammatory biomarker high-sensitivity C-reactive protein

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Abstract

Purpose: This study aimed to examine the relationship of perivascular adipose tissue (PVAT) stranding in coronary computed tomography angiography (CCTA) with high-sensitivity C-reactive protein (hsCRP) and the determinants of PVAT stranding in coronary artery disease (CAD) patients.

Material and methods: This retrospective cross-sectional study was done by collecting data from CAD patients who were referred to Rajaie Cardiovascular Centre between January 2018 and September 2020, with CCTA and hsCRP test 72 hours apart from the CCTA. PVAT stranding was defined as irregular obscuration of PVAT adjacent to the coronary arteries. An attempt was made to find a correlation between included variables and PVAT stranding by comparing them between 2 groups: patients with and without PVAT stranding.

Results: From 92 patients, 31 participants had PVAT stranding, and statistically significant higher levels of hsCRP were detected in them ($p = 0.007$). We demonstrated significantly higher prevalence of history of hyperlipidaemia (OR = 3.83, $p = 0.029$), high-risk plaque features (OR = 11.80, $p = 0.015$), and obstructive coronary luminal stenosis (OR = 3.25, $p = 0.025$) in patients with PVAT stranding. Also, significantly higher PVAT attenuation was detected in patients with PVAT stranding ($p < 0.001$) independently from mean attenuation of epicardial fat.

Conclusion: PVAT stranding could be used as a novel non-invasive marker in CCTA of CAD patients. More studies focusing on patient outcomes are required to better evaluate the reliability and prognostic value of this marker.

Key words: perivascular adipose tissue, coronary computed tomography angiography, high-sensitivity C-reactive protein, coronary artery disease.

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Authors' contribution:
A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

Introduction

Coronary artery disease (CAD) is the most common cause of death and resultant consequences, worldwide, and its social burden is forecasted to increase throughout the upcoming decades [1]. Despite growing evidence in primary and secondary prevention, significant residual cardiovascular risk persists [2]. Novel diagnostic methods allowing recognition of "vulnerable patients" will enable utilization of targeted therapies in primary or secondary prevention, to prevent the progression of clinical cardiovascular events such as myocardial infarction [3].

Inflammation has been considered a key factor in atherogenesis and the development of vulnerable atherosclerotic plaque [4,5]. It is known that systemic inflammatory markers and, in particular, high-sensitivity C-reactive protein (hsCRP) correlate with cardiovascular risk prediction, independently of definite cardiovascular risk factors [6]. Circulating inflammatory biomarkers such as hsCRP are excellent for the diagnosis of systemic inflammation, which is commonly associated with coronary inflammation; nevertheless, they are also often accompanied by other systemic or local inflammations such as infectious processes and other inflammatory conditions [7]. In addition, prior studies showed the potential use of non-invasive imaging, using positron emission tomography (PET) in the assessment of coronary artery inflammation [8], but this modality is expensive and of limited availability.

Recent studies focused on the role of coronary computed tomography angiography (CCTA) in the detection of coronary inflammation using perivascular adipose tissue (PVAT) attenuation. Epicardial adipose tissue (EAT) is located between the myocardium and the visceral layer of the pericardium, and PVAT is part of the EAT close to the coronary arteries with integration to the vascular wall to various degrees, depending on vessel size [3,9]. PVAT acts as a sensor of early vascular disease signals as coronary artery inflammation induces a shift of PVAT's composition from lipid to aqueous phase leading to increased CT density around the inflamed arteries [3]. This PVAT's composition changes can be seen visually as fat stranding.

Some recent studies have demonstrated correlation of higher PVAT attenuation as a novel surrogate measure of coronary inflammation with CAD and severity of CAD, presence of atherosclerotic plaques and high-risk plaques [10-12], culprit lesions in patients with acute coronary syndrome (ACS) [13], and acute plaque rupture and spontaneous coronary artery dissection [14]. Also, previous studies showed that utilization of PVAT attenuation leads to a significant improvement in cardiac risk prediction and re-stratification beyond traditional risk factors and carries striking prognostic value in both primary and secondary prevention [15-17].

Although prior studies have shown the aforementioned findings, more studies seem necessary to examine PVAT to clarify the role of this index in risk assessment in CAD patients. The majority of studies that examined perivascular adipose tissue have focused on quantifying dynamic spatial changes in PVAT as fat attenuation index in detection of pericoronary inflammation [9-13,16,17]. Despite the significant role of fat density, qualitative changes such as fat stranding could be helpful in this manner [14]. In this study, we focused on PVAT stranding in CCTA, and we seek to evaluate the relationship between it and the inflammatory marker hsCRP (as a known cardiovascular risk factor), as well as the determinants of PVAT stranding in CAD patients.

Material and methods

Study design and participants

This investigation was performed as a retrospective cross-sectional study collecting data from CAD patients who were referred to Rajaie Cardiovascular, Medical & Research Centre between January 2018 and September 2020. Patients with CCTA and hsCRP test 72 hours apart from the CCTA were included. Exclusion criteria for the present study were participants with prior history of revascularization such as coronary stenting or coronary artery bypass grafting and patients with a history of systemic or local inflammatory disorders including endocarditis and myocarditis, because of their impact on hsCRP levels. Also, we excluded patients with suboptimal image quality and with a history of consumption of statins, due to their effects on pericoronary inflammation and epicardial adipose tissue attenuation [18]. Informed consent was obtained from all participants, and the Institutional Research Ethics Committee of the School of Medicine at Iran University of Medical Sciences approved the study (No: IR.IUMS.FMD.REC.1399.247).

Study variables and measurement

For the purposes of this study, to evaluate the correlation of PVAT stranding with hsCRP levels and determinants of PVAT stranding in CAD patients, we collected the information of the participating patients retrospectively from their clinical records and also reviewed their CCTA images. In the next part, information about the variables extracted from patients' CCTAs will be explained in detail. Demographic information of participants including age (year) and gender (male/female); past medical history including diabetes mellitus, hypertension, hyperlipidaemia, and smoking; laboratory findings such as inflammatory markers (hsCRP and erythrocyte sedimentation rate [ESR]), troponin I level (normal/high), and lipid profiles of patients: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG), were extracted.

Image acquisition and analysis

Participants' coronary CT angiography was performed by our centre using a dual-source, 384-slice (2 × 192 detector

row) CT scanner (Somatom Force; Siemens, Forchheim, Germany). Patients received oral administration of metoprolol (25-50 mg) one hour before the scheduled scan if their resting heart rate was > 70 beats per minute, and all patients received sublingual nitroglycerin (0.3 mg) immediately before the scan. Non-contrast cardiac CT images with a 3-mm slice thickness were obtained before coronary CTA. Coronary CTA images were acquired with the scan protocol as follows: tube voltage of 70 to 120 kVp, tube current of 200 to 500 mA, gantry rotation speed of 250 ms per rotation, field matrix of 512 × 512, and scan slice thickness of 0.6 mm. As soon as the signal density level in the ascending aorta reached a predefined threshold of 150 Hounsfield units (HU), acquisition of CT data and an ECG trace were automatically started. Images were acquired after a bolus injection of 45 to 60 ml of contrast media (Iohexol, 350 mg iodine/ml, GE Health Care, Ltd. USA) at a rate of 5 to 6 ml/s, using prospective ECG triggering or retrospective ECG gating with automatic tube current modulation.All scans were performed during a single breathhold. Images were reconstructed at a window centred at 55-75% of the R-R interval. Multiplanar reformatted CCTA was used, and images were reviewed by a cardiovascular expert radiologist with 14 years of experience. All of measurements were done for the left main coronary artery, right coronary artery (RCA), left anterior descending artery (LAD), and left circumflex artery (LCX).

PVAT stranding was defined as irregular obscuration of perivascular fat adjacent to the coronary arteries [14], and the CAD patients were divided into 2 groups: patients with and without PVAT stranding. Other variables were examined in these 2 groups, and an attempt was made to find a correlation between them and PVAT stranding by comparing them between the 2 groups. We also calculated PVAT attenuation at multiple sites along the coronary arteries every 2 cm by placing a region of interest of equivalent volume (0.1 cm^3) adjacent to the coronary artery wall (Figure 1). In addition, we measured volume (cm^3) and mean attenuation value (Hounsfield units) of epicardial adipose tissue using dedicated volumetric software (Volume, Leonardo, Siemens Healthcare, Erlangen, Germany) in a semi-automated manner by tracking the visceral pericardium contour from the level of the carina to the apex of the heart at non-contrast cardiac CT. Attenuation values varying between −180 and −30 Hounsfield units (HU) were defined as fat voxels.

We classified patients with a high-risk plaque as participants having at least one of the high-risk plaque features, including positive remodeling, napkin-ring sign, spotty calcium, and low-attenuation plaque (< 30 HU), as described previously [19]. We described coronary artery stenosis according to Coronary Artery Disease – Reporting and Data System (CAD-RADS) classification [20], and defined patients with CAD-RADS 3-5 (luminal stenosis equal to and higher than 50%) as obstructive coronary artery disease. In addition, the coronary artery calcification score was quantified based on the Agatston score [21] in non-contrast cardiac CT.

Statistical analysis

We performed one sample Kolmogorov-Smirnov test to explore the normal distribution of quantitative variables, which were determined variables including laboratory findings (such as hsCRP, ESR, HDL, TG), EAT volume, coronary artery calcification and PVAT attenuation of each coronary artery did not follow a normal distribution in our study population. So, these variables presented

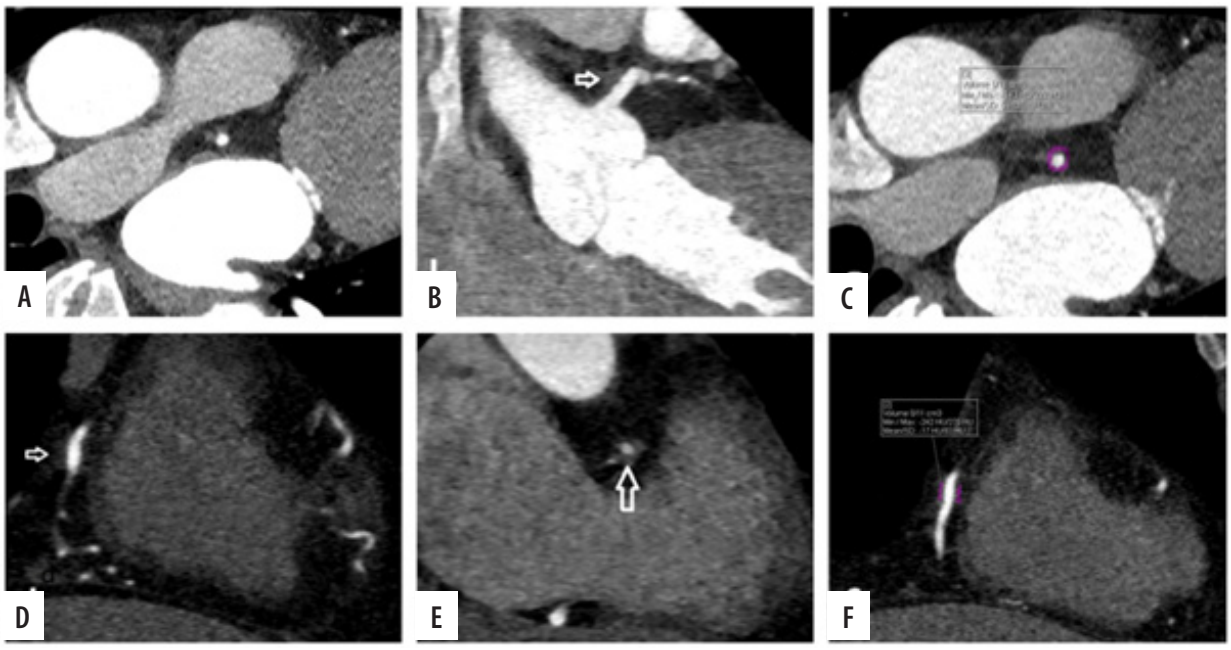

Figure 1. Examples of perivascular adipose tissue (PVAT) stranding around the left main coronary (**A-C**) and right coronary (**D-F**) arteries at their coronal (**B, D**) and axial (**A, E**) planes with calculation of their PVAT attenuation (**C, F**)

as median (interquartile range), and the nonparametric Mann-Whitney *U* test was used for comparison of them. Normally distributed numerical variables (including age, total cholesterol, LDL and EAT attenuation) were expressed as mean (standard deviation), and Student's *t*-test was used for their comparison. Furthermore, categorical variables were presented as numbers (percent), and we used the chi-square test and odds ratio and 95% confidence interval for their analysis between 2 groups. SPSS (v. 22, Chicago, IL) as our analytical software was used, and we considered $P < 5\%$ as statistically significant.

Results

Finally, 92 patients were included in the present study; their characteristics based on demographic information and their past medical histories are summarized in Table 1. Approximately one-third of them (31 participants) had PVAT stranding, and the remainder (61 participants) had no stranding in their perivascular adipose tissue. Most patients were in the age group 45 to 59 years, 49 persons were male, and the remainder (43 persons) were female. History of hypertension was more common in comparison to other past medical histories.

Table 1. Participants' characteristics based on demographics and past medical history

Variables	PVAT stranding, *n* (%)		Total, *n* (%)
	Yes	No	
Demographics			
Age groups, years			
15-29	4 (4.3)	6 (6.5)	10 (10.9)
30-44	9 (9.8)	12 (13.0)	21 (22.8)
45-59	10 (10.9)	29 (31.5)	39 (42.4)
≥ 60	8 (8.7)	14 (15.2)	22 (23.9)
Gender			
Male	18 (19.6)	31 (33.7)	49 (53.3)
Female	13 (14.1)	30 (32.6)	43 (46.7)
Past medical history			
Diabetes mellitus			
Yes	6 (9.4)	5 (7.8)	11 (17.2)
No	19 (29.7)	34 (53.1)	53 (82.8)
Hypertension			
Yes	12 (18.8)	15 (23.4)	27 (42.2)
No	13 (20.3)	24 (37.5)	37 (57.8)
Hyperlipidaemia			
Yes	9 (14.1)	5 (7.8)	14 (21.9)
No	16 (25.0)	34 (53.1)	50 (78.1)
Smoking			
Yes	6 (9.4)	9 (14.1)	15 (23.4)
No	19 (29.7)	30 (46.9)	49 (76.6)
Total	31 (33.7)	61 (66.3)	92 (100)

Determinants of PVAT stranding and their frequencies and statistics are presented in Table 2. Mean (SD) age of patients with and without PVAT stranding was 48.6 (15.8) and 49.3 (13.3), respectively; the difference was not statistically significant. Also, we detected no statistically significant differences in the gender of patients and their past medical histories (except for history of hyperlipidaemia) between the 2 groups. We demonstrated a statistically significant difference in the prevalence of history of hyperlipidaemia: 36% in patients with PVAT stranding versus 12.8% in patients without PVAT stranding (OR = 3.83, 95% CI: 1.10-13.27, $p = 0.029$), independently of their lipid profile levels.

Figure 2 shows the distribution of hsCRP (mg/l) between participants with and without PVAT stranding. According to this figure higher levels of hsCRP in patients with PVAT stranding were detected – the median (interquartile range) hsCRP in participants with and without PVAT was 4 (7.9) and 1.6 (3.4), respectively, and this difference was statistically significant ($p = 0.007$). However, no significant difference between the 2 groups in terms of ESR, another inflammatory marker, was detected. Despite the more prevalent high troponin I level in patients with PVAT stranding (29.2% vs. 10.6% in patients without PVAT stranding) this difference was not statistically considerable.

We also evaluated coronary CT angiography (CCTA) findings, which are summarized in Table 2 and Table 3. Noticeable differences in the prevalence of high-risk plaque features and obstructive coronary luminal stenosis between participants with and without PVAT stranding were found. Patients with PVAT stranding had more statistically remarkable high-risk plaque features (16.7% prevalence versus 1.7% in patients without PVAT stranding; OR = 11.80, 95% CI: 1.31-106.22, $p = 0.015$) and obstructive coronary luminal stenosis (33.3% prevalence versus 13.3% in patients without PVAT stranding; OR = 3.25, 95% CI: 1.12- 9.41, $p = 0.025$). Nevertheless, no significant differences in coronary artery calcification (CAC), including Agatston score and the number of arteries with CAC, between the 2 groups were determined.

Considering the volume and mean attenuation of EAT between patients with and without PVAT stranding, no striking differences were found, while, as presented in Table 3, significantly higher PVAT attenuation in patients with PVAT stranding around all coronary arteries was detected ($p < 0.001$). Also, in Table 3 the prevalence of PVAT stranding among coronary arteries is demonstrated, and, as can be noted, PVAT stranding is more prevalent around the left main coronary artery and RCA.

Discussion

In our study, we determined that PVAT stranding has a significant correlation with the circulating inflammatory

Table 2. Determinants of perivascular adipose tissue (PVAT) stranding and their statistics

Variables	PVAT stranding		Test statistics	*p*-value
	Yes	No		
Demographics				
Age, years	48.6 (15.8)*	49.3 (13.3)*	*t*-test = –0.198	0.844
Gender			OR = 1.34 (0.56-3.21) (Baseline: Male)	0.510
Male	18 (58.1%)**	31 (50.8%)**		
Female	13 (41.9%)**	30 (49.2%)**		
Past medical history				
Diabetes mellitus			OR = 2.15 (0.58-7.98) (Baseline: No)	0.315
Yes	6 (24.0%)**	5 (12.8%)**		
No	19 (76.0%)**	34 (87.2%)**		
Hypertension			OR = 1.48 (0.53-4.08) (Baseline: No)	0.451
Yes	12 (48.0%)**	15 (38.5%)**		
No	13 (52.0%)**	24 (61.5%)**		
Hyperlipidaemia			OR = 3.83 (1.10-13.27) (Baseline: No)	0.029
Yes	9 (36.0%)**	5 (12.8%)**		
No	16 (64.0%)**	34 (87.2%)**		
Smoking			OR = 1.05 (0.32-3.43) (Baseline: No)	0.932
Yes	6 (24.0%)**	9 (23.1%)**		
No	19 (76.0%)**	30 (76.9%)**		
Laboratory findings				
hsCRP (mg/l)	4 (7.9)***	1.6 (3.4)***	*Z* Mann-Whitney *U* = -2.690	0.007
ESR (mm/h)	12.5 (18)***	10 (13)***	*Z* Mann-Whitney *U* = -0.924	0.356
Troponin I			OR = 3.46 (0.96-12.42) (Baseline: Normal)	0.090
High	7 (29.2%)**	5 (10.6%)**		
Normal	17 (70.8%)**	42 (89.4%)**		
Total Chol (mg/dL)	155.6 (33.7)*	158.2 (42.1)*	*t*-test = –0.259	0.796
HDL (mg/dL)	34.5 (13)***	35 (9)***	*Z* Mann-Whitney *U* = –0.013	0.990
LDL (mg/dL)	97.5 (33.3)*	94.0 (30.6)*	*t*-test = 0.432	0.667
TG (mg/dL)	135 (100)***	112 (75)***	*Z* Mann-Whitney *U* = –0.800	0.423
CCTA findings				
Epicardial fat				
Volume (cm3)	76.7 (88.4)***	90.2 (63)***	*Z* Mann-Whitney *U* = –0.638	0.524
Attenuation (HU)	–73.1 (9.8)*	-76.8 (9.1)*	*t*-test = –1.746	0.084
Coronary artery calcification				
Total score	0.3 (475.6)***	0 (45.8)***	*Z* Mann-Whitney *U* = –1.029	0.303
Arteries with CAC	0 (3)***	0 (1)***	*Z* Mann-Whitney *U* = –0.932	0.351
High-risk plaque			OR = 11.80 (1.31-106.22) (Baseline: No)	0.015
Yes	5 (16.7%)**	1 (1.7%)**		
No	25 (83.3%)**	59 (98.3%)**		
Luminal stenosis			OR = 3.25 (1.12-9.41) (Baseline: CAD-RADS 0-2)	0.025
CAD-RADS 3-5	10 (33.3%)**	8 (13.3%)**		
CAD-RADS 0-2	20 (66.7%)**	52 (86.7%)**		

*Mean (standard deviation). **Number (percent). ***Median (interquartile range)

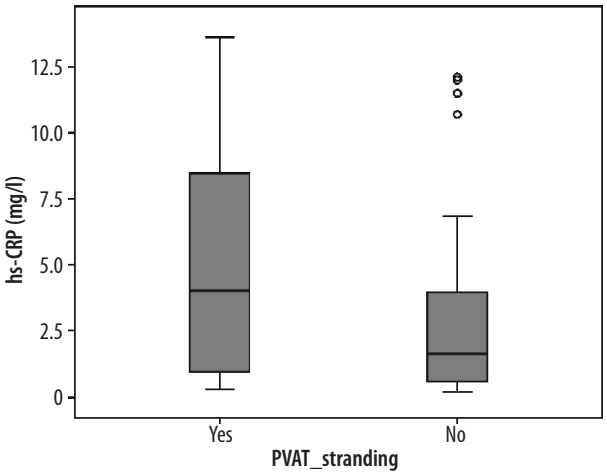

Figure 2. Distribution of high-sensitivity C-reactive protein (hsCRP) levels between participants with and without perivascular adipose tissue (PVAT) stranding

biomarker hsCRP; hence, ACS patients with perivascular fat stranding had significantly higher hsCRP levels, independently of their ESR levels (another systemic inflammatory marker). This finding contrasts with the study of Dai *et al.*, who demonstrated a poor correlation between perivascular fat attenuation and hsCRP measurements [22]. In their study, high-risk plaque features such as low attenuation plaque and napkin-ring sign were more commonly present in CAD patients with high levels of hsCRP [22]. Also, Sugiyama *et al.* showed that hsCRP level is one of the significant determinants of pericoronary fat attenuation, especially in male patients, but they did not find a relationship between hsCRP level and elevated pericoronary fat attenuation (≥ –70.1 HU), and they concluded that elevated pericoronary fat attenuation can reflect higher levels of pericoronary inflammation independently of hsCRP level [23]. In our study, we examined PVAT stranding with hsCRP level, and, as shown in Table 3, in patients with PVAT stranding, perivascular fat attenuation higher than –70 (the HU cut-off used in the Sugiyama *et al.* study) was present. This discrepancy could be due to different methods of measuring perivascular fat density in our study and theirs. We measured PVAT attenuation by placing a region of interest adjacent to the coronary artery wall, but Sugiyama *et al.* assessed pericoronary fat attenuation at proximal 40-mm segments of coronary arteries [23]. Therefore, it is not unreasonable to expect that the calculated perivascular fat attenuation in patients with PVAT stranding in our study was higher than the –70 HU cut-off. Also, some studies investigated the significant association between severity of CAD and increased serum hsCRP levels as a valuable biomarker for predicting CAD [24,25]. In addition, as mentioned before, studies have shown the importance of PVAT density in severity and predicting CAD. Therefore, the existence of a correlation between hsCRP level and PVAT stranding is not far from expectation and could indicate the greater value of PVAT stranding for diagnosing perivascular inflammation and its usefulness in cardiovascular risk assessment.

In the present study no significant differences in age, gender, and past medical histories such as DM, HTN, and smoking between patients with and without PVAT stranding were detected. However, we detected that a history of HLP correlates with PVAT stranding in ACS patients independently of current lipid profile levels. These findings are in line with a study by Sugiyama *et al.*, which showed no association between age, past medical history (including hyperlipidaemia), and lipid profile levels with elevated pericoronary fat density. But in their studies, a remarkable correlation with male sex was detected [23].

Table 3. Perivascular adipose tissue (PVAT) attenuation and distribution of fat stranding around each coronary artery

Variables	PVAT stranding		Test statistics	*p*-value
	Yes	No		
Left main artery				
Number (%)	14 (15.2)	78 (84.8)	*Z* Mann-Whitney *U* = -5.864	< 0.001
PVAT attenuation (HU)	21.5 (60)*	–60 (40)*		
Lt anterior descending artery				
Number (%)	9 (9.8)	83 (90.2)	*Z* Mann-Whitney *U* = -4.884	< 0.001
Perivascular FAI (HU)	–3 (29)*	–70 (31)*		
Circumflex artery				
Number (%)	8 (8.7)	84 (91.3)	*Z* Mann-Whitney *U* = -4.519	< 0.001
Perivascular FAI (HU)	12 (102)*	–58 (33)*		
Right coronary artery				
Number (%)	14 (15.2)	78 (84.8)	*Z* Mann-Whitney *U* = -5.877	< 0.001
Perivascular FAI (HU)	–1.5 (47)*	–73 (28) *		

* Median (interquartile range)

In addition, we demonstrated no association between PVAT stranding and high troponin levels or coronary artery calcification status such as Agatston score. However, we showed that PVAT stranding was approximately 12 times more common in patients with high-risk plaque features and 3 times more common in patients with moderate or higher luminal stenosis (CAD-RADS 3 to 5), and it was determined that PVAT stranding can occur in patients with mild or lower luminal stenosis (CAD-RADS 0-2), which is in contrast to the results of Hedgire *et al.* They found no PVAT stranding in subjects with minimal or mild stenosis (CAD-RADS 1-2) and showed significant association of elevated troponin level, younger patients, and lower Agatston score with PVAT stranding. They also presented a significantly lower number of high-risk plaque features in patients with PVAT stranding [14]. Our results are in line with Chen *et al.* [10], Yuvaraj *et al.* [11] and Sun *et al.* [26], who demonstrated significantly higher perivascular attenuation in patients with high-risk plaque features.

Furthermore, Hedgire *et al.* found a higher prevalence of RCA perivascular stranding, as we showed, and concluded that this could be due to the greater surrounding fat of RCA in comparison to other coronary arteries and its mid-segment perpendicular course to the axial acquisition, which can lead to better detection of fat stranding [14].

PVAT attenuation was significantly higher in patients with fat stranding compared to patients without fat stranding, independently of epicardial fat volume or attenuation. We measured PVAT attenuation and mean EAT attenuation in CCTA and non-contrast CT, respectively. Hence, significantly higher PVAT density in patients with fat stranding is more likely to be attributable to pericoronary enhancement suggestive of inflammation, which could strengthen the role of PVAT stranding. At Oikonomou *et al.* showed the optimum cut-off for the perivascular fat attenuation ≥ 70.1 HU as an indicator of increased cardiac mortality and a guide for early targeted primary and secondary prevention in patients [17]. Furthermore, Almeida *et al.* demonstrated excellent inter- and intra-reader agreement for measuring pericoronary fat attenuation [27]. In our study we focused on PVAT stranding as a new CCTA marker, which has been studied less, and we investigated much more perivascular fat attenuation than the cut-off ≥ –70.1 HU in patients with PVAT stranding. Two of our study limitations are its retrospective nature (which led to restricted case selection) and the small sample size. Also, in the present research, we did investigate the patient outcomes, which is of paramount importance in the evaluation of this CCTA marker. Exclusion of patients with poor image quality is another limitation of this study.

Conclusions

At present, CCTA is established as a first-line modality in the examination of suspected CAD, and due to the expansion of its application in various clinical settings, it is necessary to conduct further studies to improve its sensitivity and specificity by introducing new markers and refining its diagnostic and prognostic value in the earliest stages of coronary disease [16]. Quantitative and qualitative evaluation of PVAT in CCTA are helpful in the detection of pericoronary fat inflammation. Most previous studies have examined quantitative changes of PVAT in this field, and conversely we examined the PVAT stranding in CAD patients as a novel non-invasive marker that captures early coronary inflammation instead of or besides the fat attenuation index. According to the paucity of information about PVAT, it seems that more studies, and especially prospective research focusing on patient outcomes, are required to better evaluate the reliability and prognostic value of this marker.

Disclosure

The authors report no conflict of interest.

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