

The Effect of Periplaque Fat on Coronary Plaque Vulnerability in Patients with Stable Coronary Artery Disease – a 128-multislice CT-based Study

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ABSTRACT

Background: The role of periplaque fat (PPF), as a fragment of the total epicardial adipose tissue, measured in the vicinity of a target coronary lesion, more specifically within the close proximity of a vulnerable plaque, has yet to be evaluated. **The study aimed to** evaluate the interrelation between PPF and coronary plaque vulnerability in patients with stable coronary artery disease (CAD). **Secondary objective:** evaluation of the relationship between the total pericardial fat and markers for plaque vulnerability. **Materials and methods:** We prospectively enrolled 77 patients with stable CAD, who underwent 128-multislice computed tomography coronary angiography (CTCA), and who presented minimum one lesion with >50% stenosis. CTCA analysis included measurements of: total pericardial fat and PPF volumes, coronary plaque characteristics, markers for plaque vulnerability – positive remodeling (PR), low attenuation plaque (LAP), spotty calcifications (SC), napkin ring sign (NRS). Study subjects were divided into two categories: Group 1 – 1 marker of plaque vulnerability (n = 36, 46.75%) and Group 2 – ≥1 marker of vulnerability (n = 41, 53.25%). **Results:** The mean age of the population was 61.77 ± 11.28 years, and 41 (53.24%) were males. The analysis of plaque characteristics showed that Group 2 presented significantly longer plaques (16.26 ± 4.605 mm vs. 19.09 ± 5.227 mm, p = 0.02), remodeling index (0.96 ± 0.20 vs. 1.18 ± 0.33, p = 0.0009), and vessel volume (p = 0.027), and more voluminous plaques (147.5 ± 71.74 mm³ vs. 207.7 ± 108.9 mm³, p = 0.006) compared to Group 1. Group 2 presented larger volumes of PPF (512.2 ± 289.9 mm³ vs. 710.9 ± 361.9 mm³, p = 0.01) and of thoracic fat volume (1,616 ± 614.8 mm³ vs. 2,000 ± 850.9 mm³, p = 0.02), compared to Group 1, but no differences were found regarding the total pericardial fat (p = 0.49). Patients with 3 or 4 vulnerability markers (VM) presented significantly larger PPF volumes compared to those with 1 or 2 VM, respectively (p = 0.008). There was a significant positive correlation between PPF volume and the non-calcified (r = 0.474, 95% CI 0.2797–0.6311, p < 0.0001), lipid-rich (r = 0.316, 95% CI 0.099–0.504, p = 0.005), and fibro-fatty (r = 0.452, 95% CI 0.2541–0.6142, p < 0.0001) volumes. The total pericardial fat was significantly correlated only with the volume of lipid-rich plaques (p = 0.02). **Conclusions:** Periplaque fat volume was associated with a higher degree of coronary plaque vulnerability. PPF was correlated with lipid-rich, fibro-fatty, and non-calcified plaque-related volumes, as markers for enhanced plaque vulnerability. PPF volume, assessed with native cardiac computed tomography, could become a novel marker for coronary plaque vulnerability.

Keywords: periplaque fat volume, vulnerable coronary plaques, coronary artery disease, pericardial fat volume, CT coronary angiography

BACKGROUND

Vulnerable coronary plaques

Unstable coronary atheromas present increased risk for rupture, erosion, and thrombosis, with the consequent development of an acute coronary syndrome. The concept of “plaque vulnerability” refers to lesions that are prone to cause an acute event, which have been described as presenting a thin fibrous cap and underlying large lipid core, that leads to eccentric vascular remodeling followed by luminal narrowing and distal myocardial ischemia.¹⁻³ Several invasive and noninvasive imaging methods have been described for the assessment of high-risk vulnerable coronary lesions.⁴⁻⁷ Invasive imaging techniques used for the identification of vulnerability markers (VM) for coronary atherosclerosis include intravascular ultrasound (with description of plaque burden, remodeling index, cross sectional area, and necrotic core,) and optical coherence tomography (which measures the thickness of the fibrous arch, lipid arch, intracoronary thrombi, or macrophages).^{8,9} Computed tomography coronary angiography (CTCA) is a noninvasive method that provides visualization of the entire coronary tree, as well as the vessel lumen and wall characteristics, while offering similar accuracy in detecting coronary vulnerability as the intracoronary imaging techniques.¹⁰⁻¹² VM for coronary plaques assessed via CTCA include the presence and size of the lipid necrotic core, low attenuation plaques (LAP, density of <30 Hounsfield units), positive vessel remodeling (PR), the napkin ring sign (NRS) and spotty calcifications (SC).¹³⁻¹⁷

Epicardial fat on severity of CAD and plaque vulnerability

The total epicardial fat (EF) has been shown to be associated with the total coronary atherosclerotic burden, with the severity of coronary stenoses, and with cardiovascular risk factors. Moreover, EF is directly proportional with the rate of major adverse cardiac events in patients with known coronary artery disease.¹⁸⁻²² The epicardial adipose tissue is measured with either transthoracic echocardiography as linear thickness, or with volumetric assessment via cardiac computed tomography or magnetic resonance imaging.²³ Recent studies connected the epicardial adipose tissue with the presence of high-risk coronary plaques, defined as presenting one of the following features: low attenuation, positive remodeling, napkin ring sign, spotty calcifications; studies have also shown that patients with

high-risk plaques present a larger volume of epicardial fat, compared to those with no high-risk plaques.^{24,25}

Pericoronary and periplate fat

Pericoronary adipose tissue, as a fragment of the total epicardial fat, is located in direct contact to the coronary artery wall and has pro-inflammatory properties through its paracrine effect and local release of inflammatory cytokines, which can trigger plaque formation, progression, vulnerability, and even rupture.²⁶ Pericoronary fat (PF) has also been associated with the presence of vulnerable coronary plaques, even after adjustment for obesity and smoking.²⁷ The ratio between PF and overall EF has been linked with a higher coronary plaque volume and an increased volume of mixed and non-calcified plaques.^{28,29} The role of periplate fat (PPF), measured in the vicinity of a target coronary lesion, more specifically within the close proximity of a vulnerable plaque, has yet to be evaluated. The alternative hypothesis of the present study is that an increased volume of periplate adipose tissue, measured adjacent to a hemodynamically significant coronary lesion, is associated with a more extensive plaque vulnerability (presence of plaque vulnerability features), as assessed with the use of CTCA.

The aim of the study was to evaluate the interrelation between the periplate adipose tissue, measured in the vicinity of a significant coronary lesion, and the degree of plaque vulnerability in patients with stable coronary artery disease, who undergo noninvasive CTCA. Secondary objectives include the evaluation of the relationship between total pericardial fat and markers for plaque vulnerability.

MATERIALS AND METHODS

We conducted a prospective observational cohort study, which included 77 subjects who presented in outpatient settings, at the Cardio Med Medical Center, for symptoms indicative for coronary artery disease (chest pain, dyspnea, fatigue). All subjects underwent a complete clinical examination, 12-lead ECG tracing, two-dimensional transthoracic echocardiography, followed by 128-multislice CTCA. All patients who presented minimum one lesion with $\geq 50\%$ stenosis were enrolled in the study.

Study procedures were conducted according to the ethical principles stated in the Declaration of Helsinki, and all subjects signed a written informed consent prior to being enrolled in the study.

Subjects with high clinical probability for presenting an acute coronary syndrome (unstable angina, acute ST- or non-ST-segment elevation myocardial infarction)

TABLE 1. Patient characteristics

	Group 1	Group 2	p value
Age (years)	62.14 ± 10.97	61.41 ± 11.59	0.7791
Male gender, n (%)	26 (72.22%)	15 (34.09%)	0.0007
Risk factors			
Hypertension, n (%)	28 (68.09%)	35 (83.72%)	0.13
Hypertension, n (%)	29 (80.56%)	29 (70.73%)	0.4637
Diabetes, n (%)	8 (23.53%)	14 (34.15%)	0.4529
Peripheral arterial disease, n (%)	6 (17.65%)	5 (12.20%)	0.7364
Acute myocardial infarction, n (%)	11 (32.35%)	12 (29.27%)	0.7730
Smoker, n (%)	21 (61.76%)	23 (56.10%)	0.6198

were excluded, as they were referred for emergency invasive coronary angiography. Other exclusion criteria were acute renal failure or terminal-stage chronic kidney disease, pregnancy or lactation, allergy to iodine contrast substance, active malignancy, or refusal to provide written informed consent for study enrollment.

CTCAs were performed with a Somatom Definition 128-Slice CT equipment (Siemens Healthcare GmbH, Erlangen, Germany), and image acquisitions were analyzed for the following parameters: the overall epicardial adipose tissue volume, the adipose tissue located in the vicinity of the target coronary lesion (from herein referred to as peri-plaque fat – PPF), plaque-related features (markers for plaque vulnerability, length, degree of stenosis, volume, plaque components – necrotic core, fibro-fatty, fibrotic, and densely calcified volumes), vascular indices (remodeling index, eccentricity index).

The study population was divided into two groups, based on the presence of CT markers for plaque vulnerability (low attenuation plaque, positive remodeling, spotty calcification, napkin ring sign), as follows: Group 1 – patients with 1 marker of plaque instability (n = 36); Group 2 – patients with ≥1 marker of instability (n = 41).

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad Software, Inc., San Diego, USA), with the application of two-tailed statistical comparative testing for unpaired continuous data, or Chi square test for

categorical variables, at a statistical significance of alpha 0.05. Spearman or Pearson coefficient when appropriate, was used to describe correlation analysis.

RESULTS

From the 77 study subjects, 36 (46.75%) presented only 1 marker (Group 1), and 41 (53.24%) presented more than 1 CT marker for plaque instability. The mean age of the overall study population was 61.77 ± 11.28 years, and 41 (53.24%) subjects were males.

There were no significant differences between groups in relation to age (p = 0.779), or cardiovascular risk factors including arterial hypertension (p = 0.463), diabetes (p = 0.452), peripheral artery disease (p = 0.736), previous myocardial infarction (p = 0.773), or chronic tobacco use (p = 0.619) (Table 1). However, patients in Group 1 presented a significantly higher number of male subjects, compared to Group 2 (p = 0.0007).

The distribution of CT markers for coronary plaque vulnerability is listed in Table 2. In the first group, while there were no napkin ring signs found in the analyzed plaques, the most frequent vulnerability marker was the presence of spotty calcifications (52.78% of cases). In the second group however, the most encountered vulnerability feature was positive vascular remodeling (in 73.81% of analyzed plaques) (Table 2).

TABLE 2. Presence of vulnerability features in the study groups

	Group 1 n = 36	Group 2 n = 41	p value
Positive remodeling, n (%)	11 (30.55%)	31 (75.60%)	0.0001
Spotty calcification, n (%)	19 (52.78%)	30 (73.17%)	0.3102
Napkin ring sign, n (%)	0 (0%)	10 (24.39%)	0.0013
Low attenuation, n (%)	6 (16.67%)	19 (46.64%)	0.0114

TABLE 3. CT analysis of plaque characteristics in the study groups

Parameter	All n = 77	Group 1 1 vulnerability marker n = 36	Group 2 >1 vulnerability marker n = 41	p value
Plaque length, mm	17.76 ± 5.115	16.26 ± 4.605	19.09 ± 5.227	0.0214
Stenosis, %	56.57 ± 11.25	54.03 ± 10.06	58.8 ± 11.88	0.0575
Minimum luminal area, mm ²	0.041 ± 0.026	0.047 ± 0.025	0.036 ± 0.026	0.0543
Eccentricity index	0.36 ± 0.22	0.374 ± 0.239	0.347 ± 0.219	0.6604
Remodeling index	1.079 ± 0.298	0.9619 ± 0.200	1.182 ± 0.333	0.0009
Vessel volume, mm ³	297 ± 139.1	256.2 ± 115.9	332.8 ± 148.9	0.0272
Lumen volume, mm ³	117.4 ± 64.97	108.6 ± 57.06	125 ± 70.61	0.4250
Plaque volume, mm ³	179.6 ± 97.6	147.5 ± 71.74	207.7 ± 108.9	0.0061
Calcified volume, mm ³	30.92 ± 37.69	34.2 ± 44.57	28.05 ± 30.7	0.9091
Calcified, %	18.52 ± 21.98	21.1 ± 24.67	16.26 ± 19.35	0.3377
Non-calcified volume, mm ³	148.7 ± 95.02	113.3 ± 64.2	179.8 ± 106.9	0.0017
Non-calcified, %	81.49 ± 21.97	78.91 ± 24.64	83.75 ± 19.35	0.4032
Lipid-rich volume, mm ³	11.49 ± 17.66	5.494 ± 6.352	16.75 ± 22.28	0.0128
Lipid-rich, %	5.71 ± 7.33	3.781 ± 3.887	7.405 ± 9.093	0.0661
Fibrotic volume, mm ³	137.2 ± 87.22	107.8 ± 60.67	163 ± 98.87	0.0049
Fibrotic, %	75.77 ± 20.91	75.13 ± 23.6	76.34 ± 18.52	0.7472

CT analysis of plaque-related features

When analyzing the CT characteristics of the target coronary plaques, we found no statistically significant differences between the two groups regarding the degree of vascular stenosis ($p = 0.057$), minimum lumen area ($p = 0.054$), eccentricity index ($p = 0.660$), lumen volume ($p = 0.425$), or other plaque related volumes (Table 3). However, the results showed significantly longer plaques in patients from Group 2, with more than one vulnerability feature ($p = 0.021$), a significantly higher remodeling index (0.96 ± 0.20 vs. 1.18 ± 0.33 , $p = 0.0009$) and vessel volume ($p = 0.027$), as well as significantly more volumi-

nous plaques (147.5 ± 71.74 mm³ vs. 207.7 ± 108.9 mm³, $p = 0.006$). The analysis of plaque-related volumes revealed that patients in Group 2 presented significantly larger non-calcified volumes ($p = 0.001$), larger lipid-rich volumes ($p = 0.012$), and larger fibrotic volumes ($p = 0.004$) in the analyzed coronary plaques (Table 3).

Periplaque fat, total pericardial fat, and thoracic fat in coronary vulnerability

Patients with more than one marker for coronary vulnerability (Group 2), presented a significantly larger volume

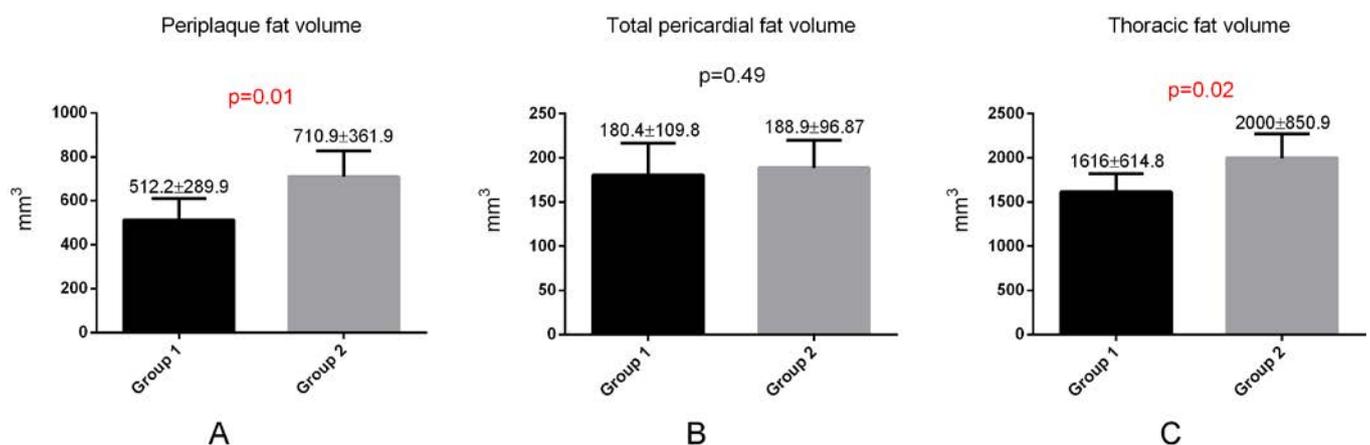


FIGURE 1. Comparative analysis between the two coronary vulnerability groups. **A** – Periplaque fat volume; **B** – Total Pericardial fat volume; **C** – Thoracic fat volume

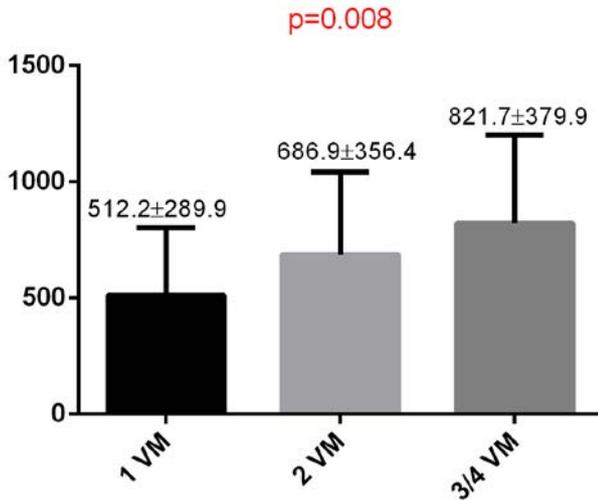


FIGURE 2. Periplaque fat (mm^3) and vulnerability degree of coronary plaques. VM – vulnerability markers

of periplaque fat (PPF) compared to Group 1 (Figure 1A). No significant differences were recorded between the two groups regarding the total pericardial fat volume (Figure 1B), but the thoracic fat volume was significantly larger in Group 2 ($p = 0.02$) (Figure 1C).

The analysis of periplaque volume based on the vulnerability degree of the coronary plaques showed that patients with 3/4 CT markers for plaque instability presented a significantly higher volume of PPF compared to those presenting one or two markers, respectively ($p = 0.008$) (Figure 2).

Correlations between periplaque fat, total pericardial fat and plaque related volumes

Linear regression analysis revealed significant positive correlations between the volume of adipose tissue located around the analyzed plaque and the following plaque-related volumes: non-calcified volume ($r = 0.474$, 95% CI 0.2797–0.6311, $p < 0.0001$), lipid-rich volume ($r = 0.316$, 95% CI 0.099–0.504, $p = 0.005$), and fibro-fatty volume ($r = 0.452$, 95% CI 0.2541–0.6142, $p < 0.0001$) (Figure 3). However, there was no significant correlation between the periplaque volume and the total plaque volume ($r = -0.12$, 95% CI -0.3475 – 0.1063 , $p = 0.27$) or the calcified volume ($p = 0.6$) (Figure 3).

The total pericardial fat was not significantly correlated with the plaque volume ($p = 0.4$), calcified volume

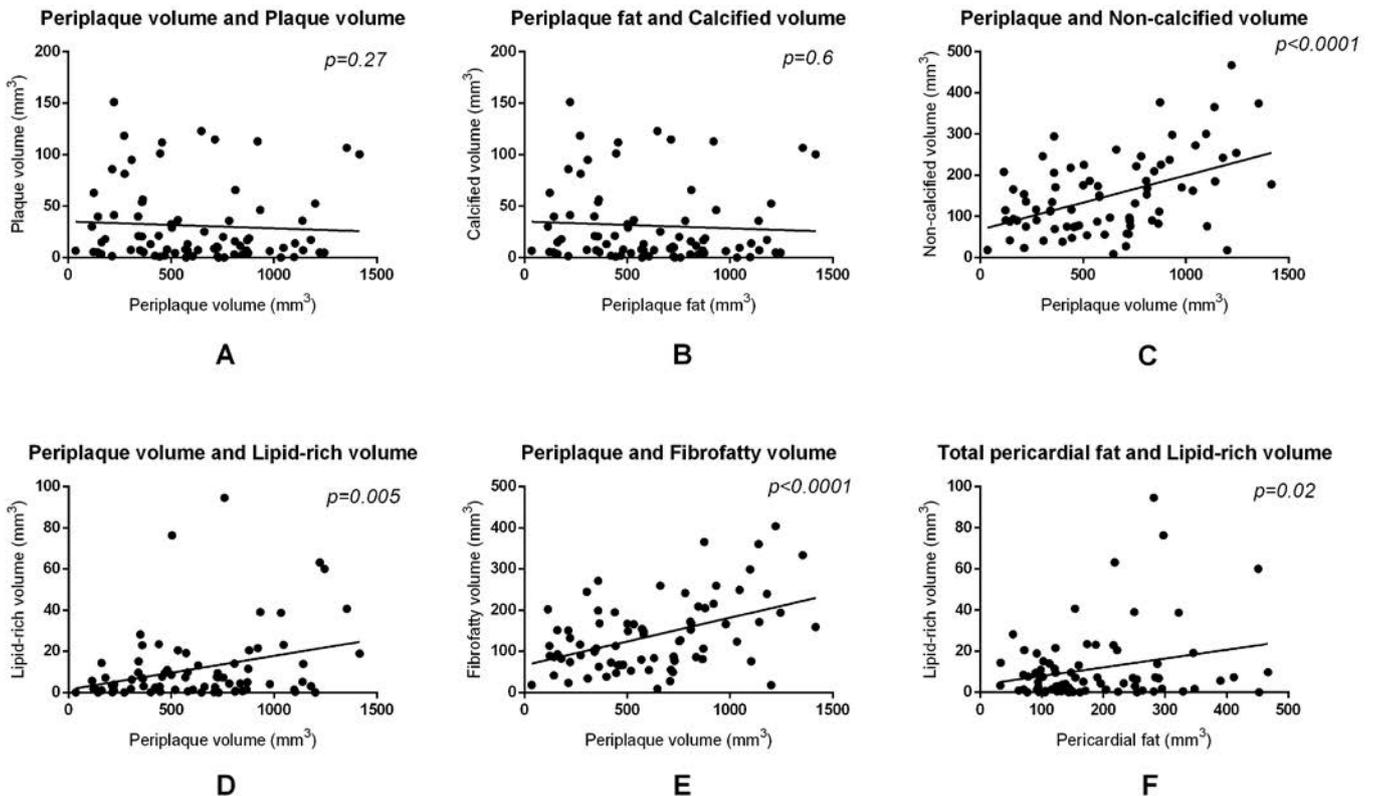


FIGURE 3. Correlations between periplaque fat volume and plaque volume (A), calcified plaque volume (B), non-calcified plaque volume (C), lipid-rich volume (D), fibro-fatty volume (E), and total pericardial fat and lipid-rich volume (F).

($p = 0.6$), non-calcified plaque volume ($p = 0.2$), or fibro-fatty volume ($p = 0.4$). However, the lipid-rich volume plaques were significantly correlated with the total volume of the pericardial fat ($p = 0.02$) (Figure 3F).

DISCUSSIONS

The present study aimed to evaluate the relationship between the peri-plaque fat volume and the presence of CT vulnerability markers for coronary plaques. The adipose tissue surrounding the heart, more specifically the epicardial and pericardial fat, has been the subject of numerous studies that included coronary artery disease patients.^{18,30} Epicardial fat represents the visceral adipose tissue between the myocardial cells and the visceral layer of the pericardial membrane, while the pericoronary or perivascular adipose tissue is observed in the vicinity of the coronary vessels. Moreover, the pericardial fat, which is similar to the subcutaneous adipose tissue, having also a common embryological origin, is located between the two layers of the pericardial membrane.³¹

Noninvasive evaluation of epicardial adipose tissue is performed with the help of 2D transthoracic echocardiography as a hypochoic space at the level of the free wall of the right ventricle during diastole, with non-contrast multidetector computed tomography, which can assess either thickness or volume of the overall EF or in various segments, such as pericoronary or peri-plaque, as performed in the present study. The gold-standard imaging technique for epicardial fat evaluation is, however, cardiac magnetic resonance imaging, which presents higher costs and low availability, therefore having limited use.³²⁻³⁴

Both the pericardial and epicardial adipose tissue have been shown to be correlated with the overall increased cardiovascular risk, as well as with the presence of high-risk coronary plaques.^{35,36} Pericoronary adipose tissue has recently emerged as a subject of interest in studies on novel cardiovascular risk factors and on promoters for coronary atherosclerosis and vulnerability.³⁷ Several studies on histopathological samples of epicardial adipose tissue have revealed that EF contains several pro-inflammatory mediators, which can contribute to the extravascular causes of atherosclerosis progression.³⁸⁻⁴⁰

The present study found that patients with significant coronary atherosclerosis, who presented high-risk coronary plaques, with more than one CT plaque vulnerability marker, presented significantly higher volumes of peri-plaque fat and thoracic fat volume compared to patients with one CT vulnerability marker (either positive remodeling, spotty calcifications, low attenuation plaque, or

napkin ring sign). Despite the previously mentioned findings, we found no significant association between a higher degree of plaque vulnerability and the total volume of the pericardial adipose tissue. A subanalysis from the Framingham heart study showed that pericardial fat and visceral abdominal fat were independently associated with measures of obesity (waist circumference, body mass index) as cardiovascular risk factors, but the association was not valid after adjustments for traditional risk factors.³⁵

In addition, when evaluating the volume of epicardial adipose tissue measured at the level of the target coronary plaque based on an increasing degree of coronary plaque vulnerability, we found that subjects with three or four CT vulnerability markers presented a significantly higher PPF volume compared to those with two or one vulnerability marker, respectively.

Although peri-plaque fat has not been studied, Hassan *et al.* sought to evaluate the relationship between the segmental epicardial fat volume, evaluated with the use of cardiac magnetic resonance (CMR), and the underlying coronary plaque characteristics in patients with stable angina. Their study included the evaluation of each coronary artery segment ($n = 8$) with the assessment of segmental adipose tissue volume (with CMR) and the evaluation of coronary plaque features via multidetector computed tomography. Their results revealed a significant correlation between segmental epicardial fat volume and increasing luminal stenosis ($p < 0.001$), and lesions with mixed plaques and low-attenuation non-calcified plaques presented significantly greater volumes of segmental epicardial fat volumes compared to lesions with calcified or CT attenuation plaques.²⁵

Our study found significant linear correlations between peri-plaque fat volume and several plaque-related volumes, which indicate a propensity towards higher vulnerability, including the non-calcified, lipid-rich, and fibro-fatty volumes. This finding suggests that a larger adipose tissue located near a hemodynamically significant coronary lesion is correlated with increased volumes of soft plaque components, which offers a higher degree of lesion instability. On the other hand, no significant correlations were found between the total plaque volume and the volume of calcified components within the analyzed plaque, and a higher extension of peri-plaque adipose tissue.

CONCLUSIONS

Epicardial adipose tissue located in the vicinity of hemodynamically significant coronary stenosis was associated with a higher degree of plaque vulnerability, as assessed

with cardiac computed tomography. Peri-plaque fat volume was significantly correlated with lipid-rich, fibro-fat, and non-calcified plaque-related volumes, as markers for enhanced plaque vulnerability.

Pericardial fat volume was not significantly associated with a higher vulnerability degree of the analyzed coronary plaque, but it was significantly correlated with the lipid-rich volume.

Peri-plaque fat volume, assessed with native cardiac computed tomography, could become a novel marker for coronary plaque vulnerability, but further larger studies on obstructive coronary artery disease are required.

CONFLICT OF INTEREST

Nothing to declare.

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