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Pericardial fat volume is related to atherosclerotic plaque burden rather than to lesion severity

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Aims We sought to explore the relationship between pericardial fat volume (PFV) and both coronary atherosclerosis (CA) extent and severity using coronary artery calcium score (CAC), computed tomography coronary angiography (CTCA), and invasive coronary angiography in patients at high to intermediate likelihood of coronary artery disease (CAD).

Methods and results Patients clinically referred to invasive angiography who underwent CTCA and CAC within 1 month before the procedure comprised the study population. PFV, CAC, atherosclerotic burden indexes [segment involvement score (SIS); segment stenosis score; three-vessel plaque; and any left main plaque], and the invasive angiography-derived CAD index were evaluated independently. A total of 75 patients were included in the study. PFV did not differ between patients with or without obstructive (stenosis >70%) CAD defined by invasive angiography (86.4 ± 31.7 vs. 77.1 ± 42.8 cm^3, $P = 0.34$), although patients with obstructive CAD had significantly higher CAC scores [636.0 (IQR 229.5–1101.0) vs. 206.0 (IQR 0.0–675), $P < 0.0001$] than patients without obstructive CAD. Patients with extensive CA (SIS > 5) had significantly larger PFV (89.9 ± 33.9 vs. 58.7 ± 33.2 cm^3, $P = 0.003$) than patients with non-extensive CA. Significant correlations were found between PFV and CAC ($r = 0.49$, $P < 0.0001$), and SIS ($r = 0.46$, $P < 0.0001$), whereas very weak correlations were observed between PFV and the CAD index ($r = 0.27$, $P = 0.02$), and between PFV and the body mass index ($r = 0.33$, $P = 0.004$).

Conclusion The main finding of the present study was the identification of PFV as more closely related to atherosclerotic plaque burden rather than to lesion severity in patients referred to invasive coronary angiography.

Keywords adipose tissue • atherosclerosis • stenosis • computed tomography • calcium • angiography

Introduction

Several studies have established a link between adipose tissue and atherosclerosis. Visceral adipose tissue (VAT) is related to insulin resistance, inflammatory markers, hypercholesterolaemia, and endothelial dysfunction.[1] Both VAT and pericardial adipose tissue (PAT) share a similar embryological origin and can release pro-inflammatory cytokines and free fatty acids that may exert harmful effects particularly in patients with established coronary artery disease (CAD) and metabolic syndrome.[2] PAT has been related to subclinical coronary atherosclerosis (CA) identified by coronary artery calcium (CAC) scoring, but also to impaired left ventricular function and even to atrial fibrillation, supporting a local structural and functional toxic effect.[3] In addition, the assessment of PAT using non-enhanced computed tomography has shown potential to predict adverse cardiac events in asymptomatic patients.[4] A paracrine effect including oxidative stress and a pro-coagulation state have been proposed as key factors involved in the pathogenesis of atherosclerosis progression in this milieu, particularly promoted given the proximity between PAT and the coronary adventitia.[5]

Nonetheless, it remains unclear whether PAT is related to lesion severity. Few studies have compared the extent of PAT using both CAC and computed tomography coronary angiography (CTCA). Robust prospective clinical data have shown that patients with non-obstructive CA have worse survival rates compared with patients with normal coronary arteries, and that the presence of extensive but non-obstructive CA portends similar cardiovascular risk than the presence of obstructive but non-extensive CA.[6–9] We

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therefore sought to explore the relationship between PAT and both CA extent and severity in patients at intermediate to high likelihood of CAD using CAC, CTCA, and invasive coronary angiography (ICA).

Methods

The present study involved patients with suspected CAD referred for ICA due to typical chest pain, dyspnoea on exertion, or atypical symptoms with positive stress test, who underwent CTCA and CAC within 1 month before the ICA. All patients were >18 years old, in sinus rhythm, without a history of contrast related allergy, renal failure, or haemodynamic instability. Other exclusion criteria comprised a history of previous myocardial infarction within the previous 30 days, percutaneous coronary intervention with stent implantation, coronary bypass graft surgery, or chronic heart failure. Coronary risk factors were defined as indicated by the Framingham risk score assessment.

CTCA was performed in all cases using a 64-slice high-definition scanner (Discovery HD 750, GE Healthcare, Milwaukee, USA), after intravenous administration of iodinated contrast (iobitridol, Xenetix 350^{TM}, Guerbet, France). A total of 60–80 mL of iodinated contrast was injected using a three-phase injection protocol. Image acquisition was performed after sublingual administration of 2.5–5 mg of isosorbide dinitrate. Patients with a heart rate of >65 bpm received 5 mg intravenous propranolol if needed to achieve a target heart rate of <60 bpm.

Image acquisition and analysis

Non-enhanced cardiac CT scans (CAC) were performed using ECG gating at 75% of the cardiac cycle, using a 2.5 mm slice thickness and a tube potential of 120 kV. All CTCA scans were acquired using prospective ECG gating applying a 100-ms padding centred at 75% of the cardiac cycle for patients with a heart rate lower than 60 bpm, a 200-ms padding centred at 60% of the cardiac cycle for patients with a heart rate between 60 and 74 bpm, and a 100-ms padding centred at 40% of the cardiac cycle for patients with a heart rate higher than 74 bpm. Iterative reconstruction was performed in all cases at 40% ASIR (Adaptive Statistical Iterative Reconstruction). Other scanner-related parameters were a collimation width of 0.625 mm and a slice interval of 0.625 mm.

Image analyses were performed offline on a dedicated workstation, using a commercially available dedicated software tool (AW 4.6, GE Healthcare) by consensus of two experienced Level 3-certified coronary CTCA observers, blinded to the clinical data.

Axial planes, curved multiplanar reconstructions, and maximum intensity projections were used at 1–5 mm slice thickness, according to the 16-segment modified American Heart Association (AHA) classification.[10] We did not use the 18-segment Society of Cardiovascular Computed Tomography classification since we aimed to use the same classification applied in the study by Min *et al.*[11] Segments with a reference diameter lower than 1 mm were not included in the analysis. Each segment was graded as follows: normal; mild stenosis (<50%); moderate stenosis (50–69%); severe stenosis (≥70%); or uninterpretable.

CT effective radiation dose was derived by multiplying the dose length product with the weighting (k) value of 0.014 mSv/mGy/cm for chest examinations, as suggested by the Society of Cardiovascular Computed Tomography.[12]

Anthropometric and pericardial fat measurements

The body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. To assess PAT, pericardial fat volume (PFV) was measured involving slices comprised within 15 mm above and 30 mm below the cranial border of the left main coronary artery. A sub-analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) study has shown that this region, which includes the PAT surrounding the proximal coronary tree [left main coronary artery, left anterior descending (LAD), right coronary artery, and left circumflex], is highly correlated to the total volume of PFV.[13] The anterior edge for volume measurements was defined by the chest wall, and the posterior edge by the aorta and the bronchus. Volumetric analysis software (AW 4.6 GE HealthCare) was used to discriminate fat from other tissues, using a threshold of −190 to −30 Hounsfield units (HU). PAT involves both epicardial (between the outer wall of the myocardium and the visceral layer of pericardium) and paracardial fat (anterior to the epicardial fat and superficial to the pericardium). Nonetheless, data from the MESA study have shown a very high correlation between pericardial and epicardial fat.[14] Furthermore, this approach avoids occasional difficulties to visualize the pericardium particularly in lean patients.

Coronary artery calcium scoring and atherosclerotic burden scores

Coronary artery calcium scoring (CAC) was calculated by an independent observer using dedicated software (SmartScore 4.0; GE Healthcare), which automatically defined the presence of calcified lesions as those with >130 HU, using the previously established Agatston method.[15]

Given that ICA was used as the reference standard, and in line with established definitions of flow-limiting stenoses, non-obstructive CAD was defined as a stenosis ≥20% but <50% in the left main coronary artery, or a stenosis ≥20% but <70% in any other epicardial coronary artery. Obstructive CAD was defined as any stenosis ≥50% in the left main coronary artery, ≥70% in any other coronary artery, or both. Angiograms with the absence of stenoses ≥20% and/or of mild luminal irregularities were considered normal.[16]

Subsequently, patients were categorized according to the atherosclerotic burden extent. For this purpose, initially patients were classified regarding CAD severity as one, two, or three-vessel distribution. Vessel distribution was defined as LAD artery and its tributaries, the left circumflex artery and its tributaries, and the right coronary artery and its tributaries. Patients with isolated 20–49% left main coronary artery stenosis were recorded as one-vessel, non-obstructive CAD, whereas those with ≥50% left main coronary artery stenosis were recorded as three-vessel obstructive CAD patients. For each vascular distribution, we determined the maximal stenosis present and classified that distribution as normal, non-obstructive CAD, or obstructive CAD. As previously established by Maddox *et al.*,[9] we created seven categories of CAD extent defined as ICA: normal; one-, two-, and three-vessel non-obstructive CAD; and one-, two-, and three-vessel obstructive CAD, hereafter referred as CAD index.

Atherosclerotic burden scores were consequently assembled as described by Min *et al.*: (i) segment stenosis score (SSS); (ii) segment involvement score (SIS); and (iii) three-vessel plaque score. Briefly, the SSS, a measure of the overall atherosclerotic burden, where each coronary segment was graded as having no to severe plaque (scores 0–3) based on the degree of coronary stenosis as aforementioned. Subsequently, the scores of all segments were summed leading to total score ranging from 0 to 48. The SIS reflected the total number of segments involved irrespective of the degree of stenosis, ranging from 0 to 16. Lastly, a binary score reflecting the absence or presence of three-vessel plaque was built.[11] Extensive CA was defined as the presence of an SIS >5, as previously reported.[11,17]

Invasive coronary angiography

Coronary angiograms were obtained in multiple projections after administration of intracoronary nitrates. All procedures were performed

in accordance to standard techniques. Quantitative coronary angiography analysis was performed by an experienced interventional cardiologist blinded to the CT data. The catheter tip was cleared of contrast for accurate calibration. Lesion measurements were performed using the 'worst' view of an end-diastolic frame.

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± SD and as median (inter-quartile range), as indicated. Comparisons among groups were performed using independent samples *t*-test or non-parametric tests (Wilcoxon signed rank test) for continuous variables with and without normal distribution, respectively. Non-parametric relationship between variables was explored using the Spearman correlation coefficient. One-way ANOVA was used to test differences between continuous variables after discrimination of patients with mild (CAC <100), moderate (CAC 100–400), and severe (CAC >400) calcification, with *post hoc* comparisons performed using Bonferroni tests. Logistic regression analysis was performed to identify potential predictors of an SIS equal or above 11 (75th percentile), including the following variables in the model (Forward Wald method): sex, age, BMI, CAD index (assessed by ICA), CAC, and PFV. All statistical analyses were performed using SPSS software, version 22 (Chicago, IL, USA). A two-sided *P*-value of <0.05 indicated statistical significance.

Results

A total of 75 patients were included in the study. The mean age was 61.9 ± 11.2 years, 54 (72%) patients were male, and 16 (21%) had diabetes. The mean BMI was 28.5 ± 3.5 kg/m^2. The mean effective radiation dose of CTCA was 4.4 ± 1.7 mSv and of CAC 0.85 ± 0.1 mSv. The median CAC was 441 (inter-quartile range 111–1012), whereas the median SIS and SSS were 9.0 (IQR 6.0–11.0) and 13.0 (IQR 9.0–17.0), respectively.

The mean PFV was 83.2 ± 35.9 cm^3, with significant gender differences (male 90.0 ± 35.0 cm^3 vs. female 65.8 ± 33.0 cm^3, $P = 0.008$; *Table 1*). Patients with extensive CA (SIS >5, $n = 59$) were older than patients without extensive CA (63.3 ± 10.8 vs. 56.6 ± 11.4 years, $P = 0.047$), and had significantly larger PFV (89.9 ± 33.9 vs. 58.7 ± 33.2 cm^3, $P = 0.003$), whereas no differences were observed between regarding BMI (28.6 ± 3.5 vs. 28.0 ± 3.7 kg/m^2, $P = 0.59$). PFV was significantly larger in patients with the presence of plaque in the three vessels (91.2 ± 33.4 vs. 44.9 ± 19.2 cm^3, $P < 0.0001$), while no significant differences were observed regarding PFV between patients with or without evidence of any plaque at the left main coronary artery (87.8 ± 33.3 vs. 76.9 ± 38.9 cm^3, $P = 0.20$). The extent of PFV according to the presence or absence of CTCA and ICA-derived indicators of extension and severity of CAD are shown in *Figure 1*.

Correlation between PFV and CA severity and extension

PFV did not differ between patients with or without obstructive (stenosis >70%) CAD defined by ICA (86.4 ± 31.7 vs. 77.1 ± 42.8 cm^3, $P = 0.34$), although patients with obstructive CAD had significantly higher CAC scores [636.0 (IQR 229.5–1101.0) vs. 206.0 (IQR 0.0–675), $P < 0.0001$] than patients without obstructive CAD.

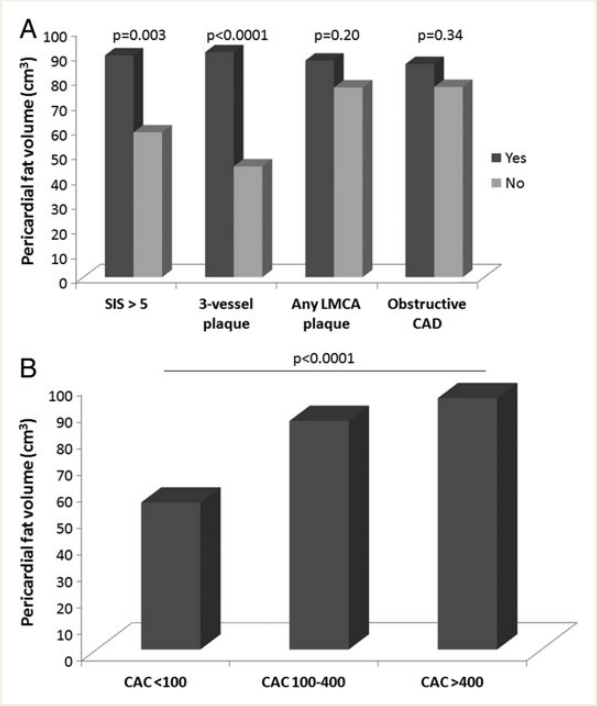

Figure 1 Extent of PFV according to the presence or absence of CTCA (SIS; three-vessel plaque; any left main coronary artery plaque) and ICA (stenosis >70%)-based indicators of extension and severity of CAD (*A*) and to the extent of CAC score (*B*).

Table 1 Pericardial fat volume according to the demographical characteristics

Demographics (*n*)	Pericardial fat volume (cm^3)	*P*-value
Male/female (54/21)	90.0 ± 35.0/65 ± 33.0	0.008
Hypertensive/non-hypertensive (52/23)	87.1 ± 34.3/74.3 ± 38.6	0.15
Hypercholesterolaemic/non-hypercholesterolaemic (49/26)	80.9 ± 34.9/87.4 ± 38.2	0.46
Smoker/non-smoker (42/33)	83.8 ± 41.6/82.5 ± 27.6	0.88
Diabetic/non-diabetic (16/59)	102.2 ± 42.2/78.1 ± 32.6	0.02

After discrimination according to the presence of mild, moderate, and severe calcification (CAC <100, CAC 100–400, and CAC >400, respectively), PFV and both CAD extension (SIS) and severity (SSS, CAD index) were significantly higher in patients with more extensive calcification (*Table 2* and *Figure 2*).

Significant correlations were found between PFV and CAC ($r = 0.49$, $P < 0.0001$), SIS ($r = 0.46$, $P < 0.0001$), and SSS ($r = 0.42$, $P < 0.0001$), whereas very weak correlations were observed between PFV and the CAD index ($r = 0.27$, $P = 0.02$), and between PFV and the BMI ($r = 0.33$, $P = 0.004$). After stratification according to sex (*Figure 3*), significant correlations persisted only among men ($n = 54$) but not among women ($n = 21$) regarding relationships between PFV and CAC (male $r = 0.59$, $P < 0.0001$; female $r = 0.25$, $P = 0.27$), SIS (male $r = 0.48$, $P < 0.0001$; female $r = 0.35$, $P = 0.12$), and SSS (male $r = 0.44$, $P = 0.001$; female $r = 0.33$, $P = 0.15$). Gender stratification lead to non-significant correlations between PFV and the CAD index (male $r = 0.21$, $P = 0.12$; female $r = 0.35$, $P = 0.12$).

No significant correlations were identified between BMI and atherosclerotic extension [CAC ($r = 0.07$, $P = 0.53$), SIS ($r = 0.10$, $P = 0.42$)] or severity [SSS ($r = 0.07$, $P = 0.55$), CAD index ($r = -0.01$, $P = 0.92$)].

Finally, after logistic regression analysis, CAC [OR 1.002 (95% CI 1.001–1.003)] and PFV [OR 1.022 (95% CI 1.001–1.042)] were the only independent predictors of an SIS ≥75th percentile (*Table 3*).

Discussion

The major finding of our study was that PAT was more closely related to atherosclerotic plaque burden than to lesion severity. A number of studies have demonstrated a relationship between PAT and CAD extension and severity.[1,3] Furthermore, additional studies using computed tomography have reported an association between epicardial adipose tissue and progression of CA.[18–20] Nevertheless, to the best of our knowledge, this is the first attempt to explore this association using validated atherosclerotic burden indexes that have been recently identified as predictors of cardiac death and myocardial infarction independently of stenosis severity.[7–9,17] In addition, given that CTCA might lead to false-positive findings particularly in patients with intermediate to high likelihood of CAD such as in our population, we evaluated lesion severity using ICA as the reference standard.

During the past few years, extensive evidence has been assembled supporting the robust prognostic value of CTCA-derived identification of non-obstructive CA as opposed to normal coronary arteries for the identification of patients at higher rates of death and myocardial infarction.[6] Indeed, Lin *et al.*[7] reported two-, three-, and six-fold higher mortality rates among patients with non-obstructive involvement of one, two, or three vessels. Particularly, the adverse prognosis of patients with extensive atherosclerotic burden evaluated using the SIS has been established in different populations.[8,11,17] Notably, the presence of extensive but non-obstructive CA has shown to portray a similar or even worse outcome than the presence of obstructive but non-extensive CA by means of both CTCA and ICA in large prospective studies.[9,11,17] In addition, a recent study has reported evidence of ischaemia in almost 20% of non-obstructive lesions and identified plaque burden estimated using CTCA as an independent predictor of ischaemia detected by invasive fractional flow reserve.[21]

On the other hand, robust evidence collected for over a decade has consistently established CAC as an independent predictor of events, with significant incremental prognostic value over conventional risk stratification algorithms.[22–24]

In our study, patients with evidence of extensive CA (SIS >5 and three-vessel plaque) had significantly higher PFV than patients with non-extensive CA, although this might be mainly driven by the relationship observed in males. It should be stressed though that the stronger correlations between PFV and CA identified among males could be at least in part related to the fewer number of females in our population. In fact, a recent study has shown similar plaque characteristics between men and women with stable angina.[25] In addition, in line with previous findings, CAC was significantly related to PFV.[26] Particularly, patients with mild CAC showed significantly lower PFV than patients with moderate to high CAC. In turn, non-significant differences were observed in PFV between patients with or without obstructive CAD. Furthermore, CAC and PFV were identified as the only independent predictors of very extensive CA (SIS ≥75th percentile), whereas neither the BMI nor the

Table 2 Differences in age, BMI, PFV, and atherosclerotic burden (assessed by CTCA) and severity (assessed by ICA) after discrimination according to the presence of mild, moderate, and severe calcification (CAC <100, CAC 100–400, and CAC >400, respectively)

	CAC <100 ($n = 18$)	CAC 100–400 ($n = 17$)	CAC >400 ($n = 40$)	*P*
Age (years ± SD)	54.0 ± 10.5	63.3 ± 8.2[a]	64.8 ± 11.1	0.002
Body mass index (kg/m^2)	28.4 ± 3.1	28.6 ± 4.5	28.4 ± 3.3	0.98
Pericardial fat volume (cm^3)	55.3 ± 27.6	86.0 ± 26.8[a]	94.6 ± 36.4	<0.0001
Segment involvement score	3.4 ± 3.6	8.1 ± 2.1[a]	10.3 ± 2.7[b]	<0.0001
Segment stenosis score	5.1 ± 6.0	12.2 ± 3.8[a]	17.7 ± 6.2[b]	<0.0001
CAD index (ICA)	2.7 ± 2.2	4.6 ± 1.7[a]	5.0 ± 1.9	<0.0001[a]

[a]Variables with significant *post hoc* (Bonferroni) differences between mild (CAC <100) and moderate (CAC 100–400) calcification.
[b]Variables with significant *post hoc* (Bonferroni) differences between moderate (CAC 100–400) and severe (CAC >400) calcification. CAD index refers to coronary artery disease index described by Maddox *et al.*[9] ICA refers to invasive coronary angiography.

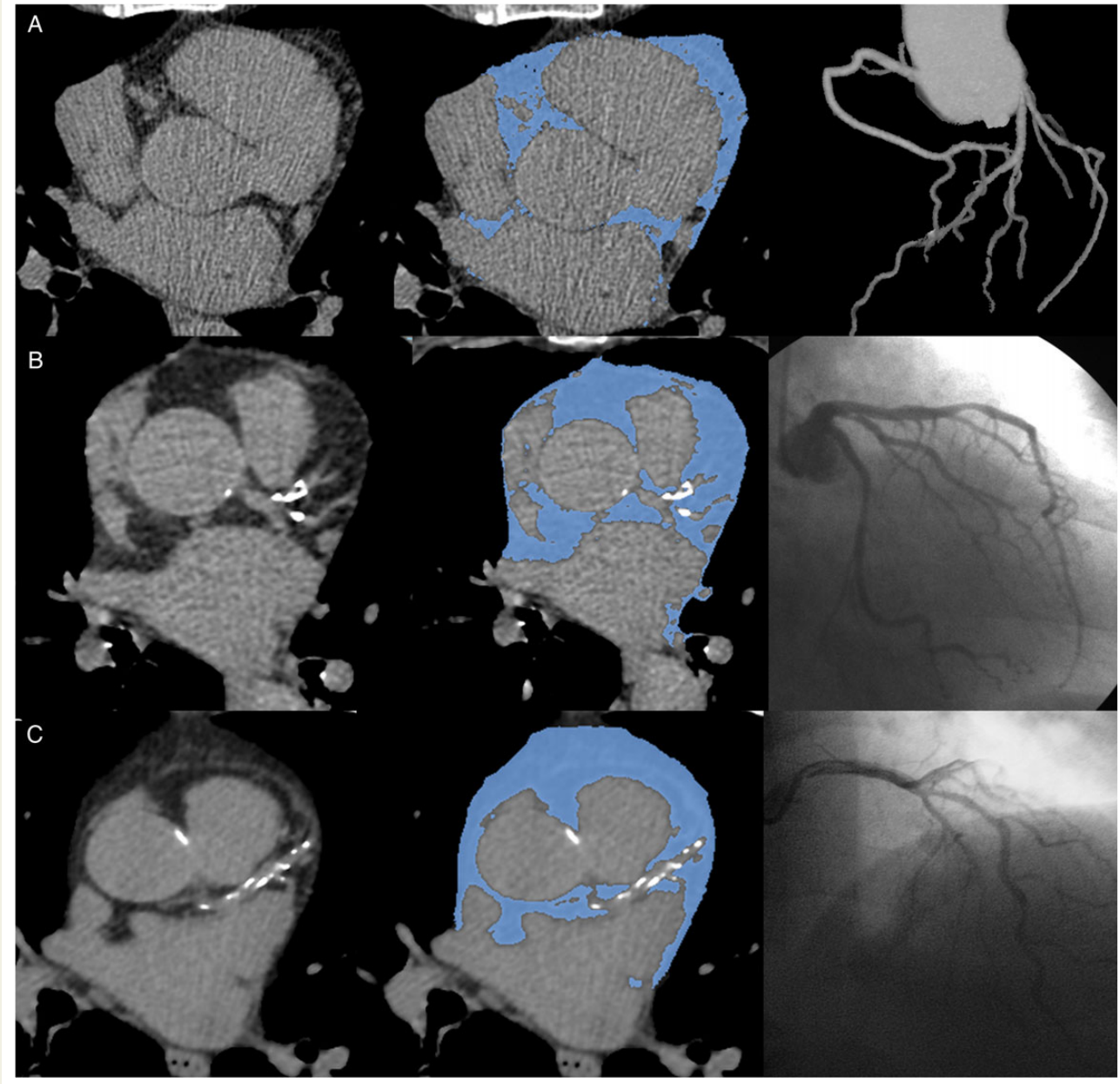

Figure 2 Relationships between PAT (in blue) assessed using non-contrast computed tomography (left and mid panels), CTCA (upper right panel), and ICA (mid and lower right panels). (*A*) Sixty-three-year-old symptomatic male with hypercholesterolaemia: PFV 38.4 cm^3; CAC score 0; and normal coronary arteries. (*B*) Seventy-eight-year-old symptomatic female with hypertension and hypercholesterolaemia: PFV 106.9 cm^2; CAC 207; SIS 7; and only mild lesions at ICA. (*C*) Eighty-year-old diabetic male with silent ischaemia: PFV 114.3 cm^3; CAC 1456; SIS 15; and only mild lesions at ICA.

CAD index (as an expression of lesion severity) did. However, using a more sensitive threshold (SIS >5), sex, age, and CAD index were the only independent predictors, although interpretation of these results should be cautious given the high prevalence of this finding in our population.

In line with previous studies including a wide range of autopsies from morbid obesity to non-obese adults who died of trauma, we identified a very weak relationship between the BMI and PAT.[27] This finding, along with the lack of correlation between BMI and atherosclerotic burden or severity, reinforces the concept that obesity might not be an atherogenic factor *per se*, but rather its association with atherosclerotic coronary disease could be a reflection of the coexistence of known risk factors for atherosclerosis in this population. Indeed, a sub-analysis of the Framingham study demonstrated an association between PAT and both cardiovascular risk factors and CAC, independently of the BMI.[28]

Recently, Mahabadi *et al.*[18] reported a closer association between epicardial adipose tissue and CA progression among patients with

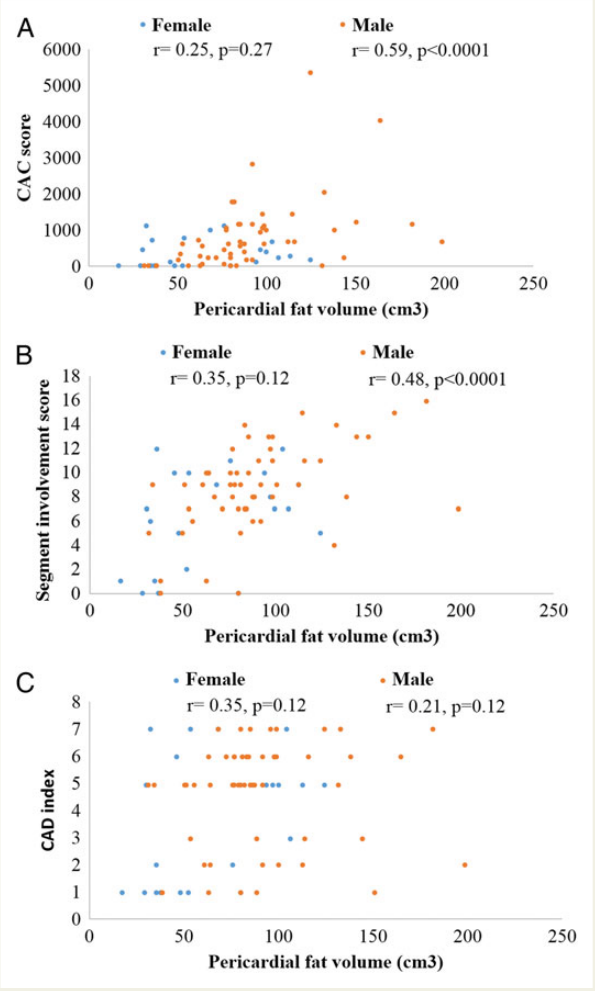

Figure 3 Relationships between PFV and CAC score (*A*), SIS (*B*), and CAD index assessed by invasive angiography (*C*). Data are discriminated according to sex.

mild CAC (thus at early stages of CA) than among those with more advanced disease. In line with these findings, we did not identify significant differences regarding PFV between patients with moderate and severe CAC.

Despite a large number of studies have explored the relationship of VAT and PAT with the presence and extent of CAD, the role of periadventitial adipose tissue in the pathogenesis of CAD remains unclear, and several mechanisms have been proposed including natural protective mechanisms such as myocardial bridging, that are typically disease-free regions isolated from epicardial fat, thus potentially avoiding transendothelial lipid permeability.[29] In the same line, using an elegant experimental porcine model fed with an atherogenic diet, McKenney *et al.* resected the portion of the epicardial adipose tissue surrounding the mid-LAD artery and performed serial intravascular ultrasound at baseline and at 3 months. Interestingly, significant plaque progression was only observed in the proximal and distal LAD, whereas no changes were observed at the mid-LAD.[30]

Overall, our findings add to the rising evidence regarding the apparent discordance between CA extension and severity. In parallel, though hypothesis generating given the small sample size, they might support the concept of CA as a multifocal disease as a result of the interplay between systemic and local factors such as shear stress and surrounding adipose tissue.[31,32] Whether simultaneous assessment of PFV during non-enhanced CT scans might or not provide an incremental prognostic value over CAC remains outside the scope of our study, although it certainly warrants further investigation.

Limitations

A number of limitations should be acknowledged. The relatively small population included might lead to selection bias, although the singular data provided (CTCA acquisitions using spectral CT, and lesion severity confirmed using ICA) should be stressed. In line with the sample size, significant gender differences regarding the PAT were observed, as previously reported in the MESA

Table 3 Logistic regression analysis according to the predefined dependent variable (SIS ≥75th percentile) and to a more sensitive dependent variable (SIS >5)

SIS ≥75%		SIS >5	
Variables in the equation			
CAC [OR 1.002 (95% CI 1.001–1.003)]		Sex [OR 6.7 (95% CI 1.05–43.5)]	
PFV [OR 1.022 (95% CI 1.001–1.042)]		CAD index [OR 2.2 (95% CI 1.4–3.3)]	
		Age [OR 1.1 (95% CI 1.03–1.22)]	
	P		*P*
Variables not in the equation			
Sex	0.82	BMI	0.45
Age	0.53	CAC	0.16
BMI	0.26	PFV	0.29
CAD index	0.18	Diabetes	0.98
Diabetes	0.59		

SIS, segment involvement score; CAC, coronary artery calcium score; PFV, pericardial fat volume; CAD index, coronary artery disease index by invasive angiography; BMI, body mass index.

study.[33] As abovementioned, PFV was measured within 15 mm above and 30 mm below the cranial border of the left main coronary artery. This approach is not only highly correlated to the total volume of PFV, but also involves the segments more commonly affected by CA.[13,34] Finally, we cannot rule out the possibility that inflation of type I error due to multiple comparisons may have confounded our results.

Conclusions

The main finding of the present study was the identification of PAT as more closely related to atherosclerotic plaque burden rather than to lesion severity in patients referred to ICA.

Conflict of interest: We declare that P.C. is a consultant of GE. There are no competing interests related to the manuscript for any of the other authors.

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