Introduction

Epicardial adipose tissue (EAT) is a visceral adipose tissue surrounding the heart and the coronary arteries. Because of its endocrine and paracrine activity, secreting pro-inflammatory and anti-inflammatory cytokines and chemokines, it has been suggested to influence coronary atherosclerosis development [1–5]. The EVASCAN (EVAuation of CT SCANner) study [6] was recently performed to establish the diagnostic accuracy of computed tomography coronary angiography compared to conventional coronary angiography (CA) in a population of symptomatic patients with a clinical indication for anatomical coronary imaging.

Using EVASCAN data, which provided precise assessment of coronary artery disease by CA and the measure of EAT by cardiac computed tomography coronary angiography in a large cohort of patients, the current analysis was performed to clarify a possible link between EAT and CAD. Our hypothesis was that EAT, as measured by...
clinical characteristics of the patients are summarized in Table 1.

Methods

Study population

We used EVASCAN data, which provided precise assessment of coronary artery disease by CA and the measure of EAT by cardiac CT to perform this study. Therefore, EVASCAN inclusion criteria were used. EVASCAN was a prospective study of correlation between CT angiography and conventional angiography in stable adults with chest pain referred for non-emergent invasive CA. Eligible patients were ≥18 years old with known or suspected CAD, able to undergo cardiac CT first, then CA within four days. The main exclusion criteria were: unstable clinical status, serum creatinine >150 µmol/L, atrial fibrillation, pregnancy and lactation. The protocol of this study complies with the Declaration of Helsinki, was approved by the institutional review board of Paris VI University and written informed consent was obtained from each patient. Classical CAD risk factors were recorded. The clinical characteristics of the patients are summarized in Table 1.

Cardiac CT and coronary angiography protocol

Patients underwent cardiac CT (684 (70.5%) patients had 64 row CT and 286 patients (29.5%) had 16 to 40 row CT) followed by conventional CA. Cardiac CT was performed using a standardized, optimized protocol for each system. All patients were in sinus rythm before cardiac CT. A beta-blocker was recommended if heart rate was >65 beats/minute.

Patients first underwent an unenhanced prospective ECG-gated acquisition for calcium scoring (Agatston score) and then a retrospective ECG-gated contrast-enhanced acquisition to explore the coronary tree and EAT. Scanning parameters varied according to the system used. Current intensity modulation was systematically applied to reduce radiation during systolic phases. The effective dose of the non-enhanced scan and the computed tomography coronary angiography was estimated from the product of the dose-length and a conversion coefficient (k = 0.017mSv/[mGy × cm]) for the chest as the investigated anatomic region [7].

A systematic reconstruction of the cardiac phases encompassing the RR interval (in 10% increments) was performed in all patients. Data were uploaded to dedicated workstations (Advantage Windows, GE; Brilliance, Philips; Leonardo, Siemens; Vitrea, Toshiba).

Conventional CA was performed using standard techniques via a femoral or radial approach [8]. All studies were performed using digital equipment. Multiple projections were obtained as deemed necessary by the angiographer.

Cardiac CT and CA interpretation

Cardiac CT and CA were analyzed visually in separate core laboratories in a blinded manner by experienced readers unaware of the patient’s clinical information or the results of the other imaging technique.

For cardiac CT, EAT was defined as the adipose tissue between the surface of the heart and the visceral epicardium surrounding the 3 main coronary arteries. To determine EAT values, epicardial

| Table 1. Population characteristics and comparison of the presence of significant angiographic coronary artery disease. |
|---------------------------------------------------------------------------------------------------------------|
| **Characteristics** | **All patients (n = 970)** | **Presence of significant coronary artery disease** | **P** |
|---------------------|--------------------------|-----------------------------------------------|------|
|                     | **N = 239** | **N = 731** | |
| Men, n (%)          | 689 (71.03%) | 122 (51.05%) | 567 (77.56%) | <0.0001 |
| Age (yrs), mean ± SD | 60.85 ± 11.36 | 57.19 ± 12.29 | 62.05 ± 10.77 | <0.0001 |
| BMI (kg/m²), mean ± SD | 27.38 ± 4.52 | 27.09 ± 5.02 | 27.48 ± 4.34 | 0.2614 |
| Waist circumference (cm); mean ± SD | 98.75 ± 13.31 | 97.33 ± 15.40 | 99.23 ± 12.51 | 0.1601 |
| Current smoker, n (%) | 244 (25.15%) | 59 (24.69%) | 185 (25.31%) | 0.8475 |
| Diabetes, n (%)      | 244 (25.15%) | 42 (17.57%) | 181 (24.76%) | 0.0218 |
| Hypertension, n (%)  | 501 (51.65%) | 95 (39.75%) | 406 (55.54%) | <0.0001 |
| Dyslipidemia, n (%)  | 427 (44.02%) | 86 (35.98%) | 341 (46.65%) | 0.0039 |
| Familial history of CAD; n (%) | 660 (68.04%) | 159 (66.53%) | 501 (68.54%) | 0.5631 |
| Metabolic syndrome, n (%) | 62 (6.39%) | 11 (4.60%) | 51 (6.98%) | 0.1927 |
| Total cholesterol (g/L), mean ± SD | 2.09 ± 1.04 | 2.09 ± 0.92 | 2.09 ± 1.07 | 0.9546 |
| LDL cholesterol (g/L), mean ± SD | 1.24 ± 0.73 | 1.25 ± 0.64 | 1.24 ± 0.75 | 0.9163 |
| HDL cholesterol (g/L), mean ± SD | 0.54 ± 0.29 | 0.59 ± 0.32 | 0.53 ± 0.28 | 0.0255 |
| Calcium scoring, median [IQR] | 15.50 [0.00; 331.00] | 0.00 [0.00; 9.00] | 82.00 [6.00; 626.00] | <0.0001 |
| Calcium scoring; mean ± SD | 379.72 ± 840.59 | 72.43 ± 275.58 | 539.28 ± 980.08 | <0.0001 |
| LVLW EAT thickness (mm); mean ± SD | 2.58 ± 2.31 | 2.08 ± 2.05 | 2.74 ± 2.37 | 0.0001 |
| RVLW EAT thickness (mm); mean ± SD | 5.38 ± 3.05 | 4.77 ± 2.73 | 5.58 ± 3.13 | 0.0004 |
| LVLW EAT thickness ≥2.8 mm, n (%) | 427 (44.02%) | 83 (34.73%) | 344 (47.06%) | 0.0009 |
| RVLW EAT thickness ≥3.3 mm, n (%) | 405 (41.75%) | 77 (32.22%) | 328 (44.87%) | 0.0005 |

BMI = body mass index; CAD = coronary artery disease; LDL = low-density lipoprotein; HDL = high-density lipoprotein; LVLW = left ventricle lateral wall; EAT = epicardial adipose tissue; RVLW = right ventricle lateral wall.

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Epicardial Fat, an Atherosclerosis Risk Factor

Results

Patients characteristics
Between June 2006 and June 2008, 40 centres prospectively enrolled 1254 patients; data from 970 were used in the present analysis. The patients excluded from the analysis had either incomplete, poor quality or missing Cardiac CT or CA, missing data for EAT thickness or withdrew consent. The baseline characteristics are shown in Table 1. The mean age was 61 ± 11 years and 71% were male. The main cardiovascular risk factors were familial history of CAD in 60% of patients, treated hypertension in 52% of the patients, dyslipidaemia in 44% of the patients, current smoking in 25% of the patients and diabetes in 25% of the patients. Mean BMI was 27.4 ± 4.3 kg/m2 and waist circumference was 99 ± 13 cm.

EAT thickness measured by cardiac CT for the entire study sample was 2.58 ± 2.31 mm for the LVLW and 5.38 ± 3.05 mm for the RVLW.

The reproducibility of EAT measurements in our study was high both in terms of intra- and inter-observer variability (correlation coefficients: 0.89 and 0.74 respectively).

Epicardial fat thickness and presence of angiographic CAD

Seven hundred and thirty one patients (75%) were found to have significant CAD on coronary angiography. Their clinical and CT findings were compared to the remaining two hundred and thirty nine patients without significant CAD.

Baseline characteristics of the 2 groups (with or without CAD) are listed in Table 1.

Patients with angiographic evidence of CAD were more frequently males, older, with a higher prevalence of conventional risk factors (diabetes, hypertension, dyslipidaemia) although the prevalence of current smoking, the average BMI, waist circumference and metabolic syndrome were not different from patients without CAD. Total cholesterol and low-density lipoprotein cholesterol were similar among groups (probably because of a high prevalence of statin use). However, HDL levels were lower.

Patients with angiographic CAD had thicker EAT on both left and right ventricle lateral walls, when compared with patients without CAD (2.74 ± 2.4 mm vs. 2.08 ± 2.1 mm; p = 0.0001 for LVLW and 5.58 ± 3.1 mm vs. 4.77 ± 2.7 mm; p = 0.0004 for RVLW). Calcium scoring mean was also higher in patients with angiographic CAD (539.28 ± 980.08 vs. 72.43 ± 275.58; p < 0.0001). (Table 1).

The odds ratio (OR) for a patient with a LVLW EAT value ≥ 2.8 mm to have CAD was 1.67 (95% CI 1.23 to 2.26). This relation remained significant after adjusting for CAD risk factors (OR = 1.46 [1.03–2.08], p = 0.0326) (Table 2). Unlike LVLW EAT; the OR for a patient with a RVLW EAT value ≥ 5.5 mm to have CAD did not remain significant after adjusting for CAD risk factors (OR = 1.38 [0.97–1.98], p = 0.0757).

The probability of a stenosis on angiography increased with increasing LVLW EAT thickness. In the first tertile of EAT thickness, the prevalence of at least one significant coronary artery stenosis was 68.9% (n = 221). In the second and the third tertiles, the prevalence rose to 75.9% (n = 249) and 81.3% (n = 261), respectively (P for trend = 0.0002) (Table 3 and Figure 1).

Simple linear regression analysis demonstrated that epicardial fat thickness was correlated with degree of coronary stenosis OR = 1.67, p = 0.0009 but not with waist circumference: OR = 1.01, p = 0.16 and BMI: OR = 1.02, p = 0.26 in CAD subjects. The independent relation of epicardial fat thickness, waist circumference and BMI with coronary stenosis was then assessed by a multiple regression analysis in CAD subjects. Epicardial fat thickness was the most significant independent correlate of degree of coronary stenosis, dependent variable in CAD subjects. (Table 4).

Epicardial fat and extent of angiographic CAD

Increased LVLW EAT thickness correlated positively with the severity or extent of CAD (Figure 2); LVLW EAT thickness mean was 2.08 ± 2.1 mm for the patients with no or minimal vessel...
disease, 2.43±2.4 mm for the patients with single vessel disease, 2.65±2.2 mm for patients with 2 vessel disease or left main disease and 2.95±2.5 mm for patients with 3 vessels disease or left main + right coronary artery disease (p for trend = 0.0001).

Moreover, patients with multivessel disease had more often a LV wall EAT thickness >2.8 mm. 83 (34.73%) patients with no or minimal vessel disease had LVLW EAT thickness ≤2.8 mm and 177 (51.45%) patients with three vessels disease had a LVLW EAT thickness >2.8 mm. This relation was better with calcium scoring (Figure 2).

Diagnostic performance of EAT and calcium scoring

On receiver operating characteristic (ROC) curve analysis, the best cut-off for LVLW EAT thickness to predict the presence of a significant coronary stenosis was 2.8 mm. LVLW EAT thickness ≤2.8 mm had a sensitivity of 46.1%, specificity of 66.5%, positive predictive value of 80%, and negative predictive value of 28.8%. The area under the curve was 0.58. The best cut-off for RVLW was 5.3 mm. RVLW EAT thickness ≥5.3 mm predicted the presence of significant coronary stenosis, with sensitivity of 45.1%, specificity of 67.9%, positive predictive value of 81.1%, and negative predictive value of 28.9%. The best cut-off for calcium scoring was 24 (Agatston score). Calcium scoring >24 predicted the presence of significant coronary stenosis, with sensitivity of 62.3%, specificity of 85.1%, positive predictive value of 89%, and negative predictive value of 54.2%. The area under the curve was 0.76 (Figure 3). Conventional cardiovascular risk factors ROC curve was determined and was added to LVLW EAT and calcium scoring measurement. Areas under the curve, sensitivity, specificity, positive and negative predictive values are summarized in Table 5. LVLW EAT thickness and calcium scoring were statistically associated (p = 0.0125).

Discussion

The present study sought to determine the link between EAT and CAD using data from the EVASCAN study [6], a large multicenter prospective study originally performed to establish the diagnostic accuracy of CTCA compared to conventional coronary angiography in a population of symptomatic patients with a clinical indication for anatomical coronary imaging.

This study confirmed that EAT thickness of left ventricle wall was associated with CAD and an independent predictor of CAD. Interestingly, we found that, even though mean right ventricle wall EAT was thicker than left ventricle wall EAT, EAT of the left

Table 2. Logistic regression analysis of the association between risk factors and presence of significant angiographic CAD.

| Risk Factor                               | Univariate analysis | Multivariate analysis |
|-------------------------------------------|---------------------|-----------------------|
|                                           | OR [95%CI]          | P                     |
|                                           |                     |                       |
| Men                                       | 3.32 [2.44–4.51]    | <0.0001               |
| Age                                       | 1.04 [1.02–1.05]    | <0.0001               |
| BMI                                       | 2.43±2.4 mm         |                       |
| Current smoker (yes vs. no)               | 1.02 [0.99–1.05]    | 0.2614                |
| Diabetes (yes vs. no)                     | 1.03 [0.74–1.45]    | 0.8482                |
| Hypertension (yes vs. no)                 | 1.54 [1.06–2.24]    | 0.0226                |
| Dyslipidemia (yes vs. no)                 | 1.90 [1.41–2.56]    | <0.0001               |
| Family history of CAD (yes vs. no)        | 1.56 [1.15–2.10]    | 0.0041                |
| Metabolic syndrome (yes vs. no)           | 1.10 [0.80–1.50]    | 0.5632                |
| LVLW EAT (≥2.8 vs. <2.8 mm)               | 1.67 [1.23–2.26]    | 0.0009                |

OR = odds ratio; CI = confidence interval; other abbreviations as in Table 1.

Table 3. Association between angiographic coronary artery disease and left ventricle lateral wall EAT thickness tertiles.

| Tertile | Men; n (%) | Age (yrs.; mean ± SD) | BMI; mean ± SD | Current smoker; n (%) | Diabetes; n (%) | Hypertension; n (%) | Metabolic syndrome; n (%) | Calcium scoring; median [IQR] | Presence of angiographic CAD; n (%) |
|---------|------------|-----------------------|----------------|-----------------------|----------------|-------------------|--------------------------|-------------------------------|----------------------------------|
| T1      | 230 (71.65%) | 57.34±11.77           | 26.51±4.73     | 108 (33.64%)          | 66 (20.56%)    | 144 (44.86%)      | 146 (45.48%)            | 4.0 (0.0; 180.0)              | 221 (68.85%)                     |
| T2      | 223 (67.99%) | 61.36±10.92           | 27.74±4.50     | 67 (20.43%)           | 76 (23.17%)    | 179 (54.57%)      | 149 (45.43%)           | 24.0 (0.0; 422.0)             | 249 (75.91%)                     |
| T3      | 236 (73.52%) | 63.91±10.38           | 27.90±4.19     | 69 (21.50%)           | 81 (25.23%)    | 178 (55.45%)      | 132 (41.12%)           | 37.0 (0.0; 406.0)             | 261 (81.31%)                     |

P = 0.0001, 0.0012, 0.0170, 0.0024, 0.0326.
ventricle but not the right ventricle wall was associated to CAD. Whether this association is driven by a functional or mechanical cause is unclear and further physiopathological studies need to be done.

Second, EAT thickness was well correlated to the severity of angiographic CAD. The greater the LVLW EAT thickness, the greater the probability of multivessel disease. Thirdly, EAT thickness was not associated with BMI and waist circumference and was the best predictor of CAD. Finally, when studying EAT as a diagnostic screening tool, it had poor performance, lower than calcium scoring. Adding EAT measurement to calcium scoring did not improve significantly the ROC curve.

There are two main implications of the present results. First, from a pathophysiologic perspective, the association between EAT and angiographic CAD is consistent with the hypothesis that epicardial fat may play a role in the genesis of CAD. EAT is the visceral fat depot of the heart. It is a metabolically active organ with anatomical and functional contiguity to the myocardium as it is located along the coronary arteries on the surface of the ventricles and the apex of the heart [10]. Because of its close proximity, epicardial fat can locally affect the heart and coronary arteries through vasocrine or paracrine secretion of a number of bioactive molecules and pro-inflammatory cytokines [11–13]. In fact, excess accumulation of epicardial fat was reported to be a stronger coronary risk factor than the distribution of other body fat [14]. On the basis of these findings, several clinical studies have investigated EAT as a cause of CAD, finding that EAT thickness and volume strongly correlated with atherosclerosis and coronary artery calcium score, both of which are characteristic of plaques and CAD [1–5]. Echocardiographic studies have suggested that EAT was neither strongly associated with the incidence of major adverse cardiovascular events in patients with CAD, nor associated with coronary artery stenosis [15–17]. More recently, a meta-analysis by Xu et al. [18], of 15 case-control studies and one case section study (N = 2872 patients) found a positive association between EAT thickness and volume and the presence of CAD. Our study confirms this association.

In addition to being associated with the presence of CAD, EAT has also been associated with fatal and nonfatal coronary events in the general population, independently of conventional cardiovascular risk factors [19]. As such, the presence of EAT may complement information from cardiac computed tomography over and above the CAC scoring. These findings are consistent with the observation that EAT is strongly associated not only with the presence, but also with the severity of CAD. Whether this association is driven by functional or mechanical causes is still unclear and further physiopathological studies with molecular insights for this relation are needed. While additional information on the biological profile of our patients, including biomarkers of inflammation, would have been useful they were not available since our data were obtained in routine medical care. Nevertheless, recent studies have shown that increased EAT thickness was associated with low grade systemic inflammation [20] and that orosomucoid secretion by EAT could be a possible indicator of endothelial dysfunction in diabetes mellitus [21]. Moreover, Hirata et al. showed that inflammatory cell infiltration was

Table 4. Multivariable correlates of degree of coronary stenosis in CAD subjects.

|                               | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                               | OR [95%CI]          | P                     | OR [95%CI]          | P                     |
| BMI                           | 1.02 [0.99–1.05]    | 0.2614                | 0.99 [0.92–1.06]    | 0.7239                |
| Waist circumference           | 1.01 [0.99–1.03]    | 0.1604                | 1.01 [0.99–1.04]    | 0.3013                |
| LVLW EAT (≥2.8 vs. 2.8 mm)    | 1.67 [1.23–2.26]    | **0.0009**            | 1.67 [1.08–2.57]    | **0.0197**            |

Abbreviations as in Table 1.

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Figure 2. Association of left ventricle lateral wall (LVLW) epicardial adipose tissue (EAT) thickness and calcium scoring between patients with none or minimal coronary artery disease, 1, 2 or 3 vessel disease. Abbreviations as in Figure 1. Mean calcium scoring (Agatston score) and mean LVLW EAT thickness (mm) and 95% confidence intervals [95% CIs] in patients with no significant angiographic coronary artery disease, 1, 2 or 3 vessel disease.
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Figure 3. Receiver operating characteristic curves. Abbreviations as in Figure 1; CV = cardiovascular.
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enhanced in EAT, but not in subcutaneous fat, in patients with CAD [22]. Chronic inflammation in epicardial fat may participate in the pathogenesis of coronary atherosclerosis and therefore, it may be interesting to combine EAT abundance and biological markers to improve the identification of patient at risk of CAD events.

We reported an association between EAT and calcium scoring. Whether EAT could influence calcium scoring is unclear. Previous studies have shown that EAT correlates with the extent of CAC [23–25]. Alexopoulos et al. [3] found that larger EAT volumes were associated with the presence of plaques with a non-calcified component. However that study had a wide range of EAT volumes in patients with mixed plaques. Nevertheless, this observation suggests that the release of noxious agents from EAT may sustain an active atherosclerotic process as proven by the presence of non-calcified plaques. The presence of mere CAC, instead, could represent a more advanced and stable phase of the atherosclerotic process. In support of this hypothesis, Broedl et al. [26], found that low levels of adiponectin, which is secreted locally by EAT, were associated with the presence of non-calcified or mixed coronary plaques, but not with the presence of calcified plaques. These concepts still remain speculative. It should also be noted that Greif et al. [27] found no relationship between EAT and any type of atherosclerotic plaque. However, these investigators did not adjust for differences in risk factor prevalence, likely confounding their ability to detect an effect of EAT volume.

The second important implication is that, although EAT is strongly correlated to the presence and extent of angiographic CAD, it is probably of little value as a diagnostic or screening tool since other methods such as calcium scoring or computed tomography coronary angiography have far superior sensitivity and specificity. Moreover, adding EAT measurements to calcium scoring did not improve the diagnostic performance.

Conclusions

From a pathophysiologic perspective, our study demonstrated a strong association between EAT and the presence and extent of angiographic CAD. It is consistent with the hypothesis that epicardial fat may play a role in the genesis of CAD, possibly due to paracrine or vasocrine mechanisms. Although EAT is correlated to CAD, it is probably of little value as a diagnostic or screening tool since other methods such as calcium scoring or computed tomography coronary angiography have far superior sensitivity and specificity.

Author Contributions

Conceived and designed the experiments: FP PG PGS. Performed the experiments: JPL SC FL DC JMJ PH. Analyzed the data: RN GC. Contributed reagents/materials/analysis tools: FP PG PGS RN GC. Wrote the paper: FP PG PGS.
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