ORIGINAL RESEARCH

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Association of pericardial adipose tissue volume with presence and severity of coronary atherosclerosis

Abstract

Purpose: This study was to investigate whether high pericardial adipose tissue (PAT) volume is related to the presence and severity of coronary artery disease (CAD).

Methods: Consecutive patients (310 patients) who underwent both dual-source 64-slice CT and percutaneous coronary angiography were recruited into this study. Waist circumference (WC), body mass index (BMI), blood biochemical variables, coronary artery calcium (CAC) score and Gensini score were measured. Pericardial adipose tissue (PAT) volume was determined by dual-source CT.

Results: PAT volume was positively correlated with BMI, WC, gender (male), hypertension, diabetes, age, total cholesterol and low-density lipoprotein-cholesterol. PAT volume in CAD patients was significantly higher than that in patients without CAD ($238.36 \pm 81.21 \text{ cm}^3$ vs. $200.13 \pm 72.34 \text{ cm}^3$). PAT volumes in patients with multi-vessel lesions were significantly higher than those with one-vessel lesions ($P < 0.001$). A significant correlation between PAT volume and CAC score ($r = 0.305$, $P < 0.001$) was found. PAT volume was an independent factor affecting Gensini score.

Conclusion: PAT volume was significantly correlated with traditional cardiovascular risk factors, the severity of coronary atherosclerosis and the number of stenotic coronary vessels. Thus, PAT volume may be a reliable marker to evaluate the presence and severity of CAD.

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The past decade has witnessed a renewed interest in heart adiposity, especially as the result of rapid development in the field of noninvasive imaging, which has made it possible to quantify ectopic fat masses and contents with improved accuracy [1]. Pericardial adipose tissue (PAT) is the true visceral fat deposited around the heart, particularly around coronary arteries. PAT thickness and volume can be quantified by echocardiography, computed tomography (CT) or magnetic resonance imaging [2-5]. PAT, as well as abdominal visceral adipose tissue, is a rich source of bioactive adipocytokines that play important roles in the development of atherosclerosis and the occurrence of cardiovascular events [6-8]; however, the progressive association between the quantity of fat and disease severity, in terms of the extent of plaque calcification and the number of vessels involved, is less obvious. Volume of PAT, determined by cardiac CT, has been shown to have superior reproducibility and accuracy as compared with thickness and area measurements determined by echocardiography [9-10]. Moreover, the images of cardiac CT can also be used to score coronary artery calcium (CAC); a sensitive marker of atherosclerosis burden [11-12]. The aim of the present study was to investigate the correlation among PAT volume, cardiovascular risk factors and severity of coronary atherosclerosis in patients with suspected coronary artery disease (CAD), quantified by 64-slice dual-source CT.

Materials and Methods

Patient selection

This study was approved by the local institutional review board and all participants gave written informed consent. A total of 354 consecutive patients, undergoing both dual-source 64-slice computed tomography coronary angiography (CTCA) and percutaneous coronary angiography due to suspected CAD, were retrospectively recruited into this study from December 2006 to January 2010. CTCA was performed in all patients within one month before or after percutaneous coronary angiography. Exclusion criteria were as follows: contrast agent allergy, thyroid dysfunction, severe arrhythmia, cardiac surgery, severe valvular heart diseases, hydropericardium serum and unfavorable CT images ($n = 44$) for the measurement of PAT volume. Finally, 310 patients (212 males and 98 females; mean age: 62.69 ± 10.78 years; range: 34-90 years) were included in the final analysis.

Clinical information was obtained using a standardized health questionnaire. Body weight (kg), waist circumference (WC; cm) and blood pressure (BP; mmHg) were measured and body mass index (BMI) was calculated as a marker of obe-

sity. On admission, fasting peripheral venous blood was collected and fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) were measured (Table 1).

Diagnostic Criteria

Diagnostic criteria for hypertension were as follows: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or patients had a history of anti-hypertensive treatment. Diagnostic criteria for diabetes were as follows: FBG ≥ 7.0 mmol/L, 2-h postprandial blood glucose ≥ 11.1 mmol/L or patients were treated with insulin or glucose-lowering drugs. BMI of ≥ 24 kg/m² was defined as overweight and BMI of ≥ 28 kg/m² as obese. According to the Guideline for Prevention of Dyslipidemia in Chinese Adults, metabolic syndrome was diagnosed when patients met three of following criteria: 1) abdominal obesity: WC was >90 cm in males and >85 cm in females; 2) TG was ≥ 1.7 mmol/L; 3) HDL-C was <1.04 mmol/L; 4) BP was $\geq 130/85$ mmHg; 5) FBG was ≥ 6.1 mmol/L, 2-h postprandial blood glucose ≥ 7.8 mmol/L or 6) patient had a history of diabetes.

Dual-Source CT

CT scanning was performed on a dual-source 64-slice CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) using two X-ray sources for image generation. With two tubes and two detectors mounted at orthogonal orientation in the gantry, the transmission data required for the reconstruction of one slab can be acquired in half the time needed by a conventional multislice computed tomography (MSCT) system. The thoracic scan was performed during a single breath hold, which began with the coronary artery calcium scanning. The scanning volume was defined as the area from the carina to the diaphragm. A gantry rotation time of 0.33 s therefore resulted in a temporal resolution of 83 ms. Tube voltage for CT-angiography was 120 kV for both tubes, with the current of 350 mAs, gantry rotation time of 0.33 s and pitch of 0.20-0.43 adapted to the heart rate, and collimation of 64×0.6 mm. Contrast agent (80 ml, 370 mg I/ml, Ultravist, Schering, Berlin, Germany) was injected at a constant rate of 5 ml/s, followed by flushing with 40 ml of normal saline. The CT value of the area of interest at the root of ascending aorta was monitored since the beginning of contrast injection. The radiation dose for CAC scan in this study was 2.7 mSv on average.

CAC score

CAC score was computed by a radiologist on a dedicated workstation (Syngo MMWP, Siemens, Germany). The overall Agatston score [13] was documented for each coronary vessel in each patient. Coronary calcium was identified as an area of the coronary artery with the intensity of >130 HU. Rumberger CAC classification [14] was used as follows: ≤ 10 AU, minimal or nonsignificant CAC, 11-100 AU, mild CAC, 101-400 AU, moderate CAC, 401-1,000 AU, severe CAC, and > 1,000 AU, extensive CAC.

Pericardial Adipose Tissue Assessment

The volumes of pericardial adipose tissue (PAT) and epicardial adipose tissue (EAT) were measured in cubic centimeter (cm^3)

FIGURE 1. Correlation between PAT volume and EAT volume

FIGURE 2. Correlation of PAT volume and EAT volume with BMI and WC (all $P < 0.001$)

TABLE 1. General characteristics of patients (n = 310).

	Range	N (%)	(mean±SD)
Age (years)	34-90		62.69 ± 10.78
Male		212 (68.39%)	
BMI (kg/m ²)	16.56-33.95		24.13 ± 3.06
WC (cm)	63.33-130.00		86.40 ± 9.59
Hypertension		205 (66.13%)	
Diabetes mellitus		87 (28.06%)	
Smoking		121 (39.03%)	
Drinking		82 (26.45%)	
FBG (mmol/L)	3.30-14.00		5.51 ± 1.55
TC (mmol/L)	2.40-8.10		4.24 ± 0.91
TG (mmol/L)	0.44-11.54		1.80 ± 1.16
LDL-C (mmol/L)	0.65-5.30		2.07 ± 0.87
HDL-C (mmol/L)	0.59-4.73		1.49 ± 0.75
PAT volume (cm ³)	59.36-526.13		233.95 ± 75.34
<100 cm ³		12 (3.87%)	
100–200 cm ³		90 (29.03%)	
200–299 cm ³		150 (48.39%)	
≥300 cm ³		58 (18.71%)	
Gensini score	0-156.00		32.05 ± 11.27

Note: BMI = body mass index; FBG = fasting blood glucose; TC = total cholesterol; TG = triglyceride; LDL-C = low density lipoprotein-cholesterol; HDL-C = high density lipoprotein-cholesterol; PAT = pericardial adipose tissue, WC: waist circumference.

using the Volume Analysis software at a dedicated workstation (Syngo MMWP, Siemens, Germany). PAT was defined as EAT plus paracardial adipose tissue. EAT was defined as any adipose tissue located within the pericardium, while paracardial fat was defined as the adipose tissue on the external surface of the parietal pericardium, with these two components separated by the fibrous pericardium. The level of pulmonary artery bifurcation was regarded as the upper point and diaphragm as lower point for measuring PAT in the axial slices. The anterior border was outlined along the chest wall and posteriorly extending to the esophagus and the descending aorta. The region of interest (ROI) containing the heart and surrounding adipose tissues was assessed by manually tracing in the axial slices. The observer had simultaneously access to the coronal images. Hounsfield units of -250~-30 HU were believed as the isolate adipose tissue in the selected ROI. Adipose tissue within the selected volume was then automatically quantified by the software in units of cm³.

Percutaneous Coronary Angiography

Conventional coronary angiography was performed using the standard Judkins' method, via the femoral artery or radial artery approach, and at least five projections were performed in all patients. Quantitative coronary angiographic analysis was employed for calibration and measurement of coronary dimensions with a digital subtraction angiography system (INNOVA 3100, GE Healthcare, Waukesha, WI, USA) by two experienced interventional cardiologists. CAD was defined as a coronary artery stenosis of 50% or greater. The number of coronary arteries involved and the location and severity of atherosclerotic lesions were recorded. The severity of coronary atherosclerosis was defined according the Gensini's score system. A greater reduction of luminal diameter was assigned a higher score, and a proximal lesion in the left anterior descending or left circumflex artery was assigned a higher score than a distal lesion.

Statistical Analysis

Statistical analysis was carried out with SPSS version 16.0 (SPSS, Chicago, IL, USA). Continuous quantitative variables were expressed as mean $\pm$ standard deviation (SD), and binary variables were presented as percentages. Quantitative data were analyzed with independent Student's *t* test or one-way ANOVA. Age-, gender- and BMI-adjusted Pearson correlation analysis was employed to evaluate the correlations among PAT volume, traditional cardiovascular risk factors and CAC scores. The area under the receiver-operating characteristic (ROC) curve was determined to demonstrate the discriminatory power of PAT volume in the diagnosis of CAD. Multivariable linear regression models were used to assess the significance of cross-sections relations among PAT volume, traditional cardiovascular risk factors and Gensini Score. A two-tailed *p* value of < 0.05 was considered as statistically significant.

Results

Relations with PAT volume and EAT volume

In a subset of 200 patients (Fig. 1), results showed that there was a significant correlation between EAT volume and PAT volume ($r=0.92$, $P<0.001$). PAT volume and EAT volume were independently associated with BMI ($r=0.63$, $P<0.001$ for PAT volume and $r=0.57$, $P<0.001$ for EAT volume) and WC ($r=0.69$, $P<0.001$ for PAT volume and $r=0.63$, $P<0.001$ for EAT volume) (Fig. 2).

Association of PAT volume with traditional cardiovascular risk factors

The clinical characteristics of patients are shown in Table 1. PAT volumes exhibited significant correlations with other traditional cardiovascular risk factors, including BMI ($R=0.53$, $P<0.001$), WC ($R=0.26$, $P<0.001$), male gender ($R=0.21$, $P<0.001$), hypertension ($R=0.20$, $P<0.001$), diabetes ($R=0.19$, $P<0.001$), age ($R=0.16$, $P=0.006$), TC ($R=0.12$, $P=0.032$) and LDL-C ($R=0.12$, $P=0.031$).

Predictive value of PAT volume for the presence of CAD

The area under ROC of PAT volume in diagnosis of CAD was 0.65 ± 0.04 (95% CI = 0.567 to 0.738, $P=0.002$). ROC analysis also revealed that the areas under ROC of 0.54 ± 0.05 ($P=0.464$) and 0.39 ± 0.05 ($P=0.019$) for WC and BMI, respectively. Compared to WC and BMI, PAT volume represented the strongest independent risk factor for CAD. With a cut-off PAT volume of 203.05 cm^3 , the sensitivity and specificity were 64.9% and 64.3%, respectively, for predicting CAD.

FIGURE 3. (A, B purple: PAT) CT images and (C, D) CAG images of a 56-year-old male with the PAT volume of 84.66 cm^3 and no arterial lesion; (E, F, purple: PAT, [black arrow]) CT images and (G, H) CAG images of a 63-year-old female with the PAT volume of 255.23 cm^3 and multi-vessel lesion; CAG images display obvious stenosis in proximal and distal segments of LAD (G, white short arrow) and RCA (H, white long arrow).

PAT volume and coronary angiographic characteristics

PAT volumes of CAD and non-CAD patients were $238.36 \pm 81.21 \text{ cm}^3$ and $200.13 \pm 72.34 \text{ cm}^3$, respectively ($P=0.004$), among 268 patients with CAD diagnosed by percutaneous coronary angiography. There was no significant difference in PAT volume among patients with coronary lesions at different locations. The PAT volumes were strongly associated with the number of arteries involved (1-vessel lesion: $206.56 \pm 68.00 \text{ cm}^3$, 2-vessel lesions: $255.58 \pm 82.94 \text{ cm}^3$, 3-vessel lesion: $266.91 \pm 79.50 \text{ cm}^3$). PAT volumes in patients with 3-vessel lesions and 2-vessel lesions were significantly higher than those in patients with 1-vessel lesion ($P<0.001$); however, the PAT volumes were comparable between patients with 2- and 3- vessel lesions ($P=0.375$).

In our study, PAT volume increased with the increases in Gensini score and severity of coronary artery stenosis (Fig. 3). The Gensini score in patients with PAT volume of $\geq 200 \text{ cm}^3$ was significantly higher than that in those with PAT volume of $<200 \text{ cm}^3$. Especially, when the PAT volume was $\geq 300 \text{ cm}^3$, the association between PAT volume and Gensini score was more close (PAT volume $\geq 300 \text{ cm}^3$ vs. $<100 \text{ cm}^3$, Gensini score 45.86 ± 3.26 vs. 17.29 ± 5.58 , $P<0.001$). Moreover, stepwise linear regression analysis showed that PAT volume, BMI and FBG were independent risk factors for Gensini score (standardized coefficients: 0.512, 0.382 and 0.129, respectively; $P<0.001$ or $P=0.012$).

Relationship between PAT volume and CAC

In our study, a significant correlation was found between PAT volume and CAC score ($r=0.305$, $P<0.001$). CAC score ranged from 0 to 3105 AU, and the study population was divided into four groups according to Rumberger CAC classification: 0 to 10, 11 to 100, 101 to 400, and above 400. Our results showed the severity of coronary calcification was proportional to PAT volume and age, but not to BMI or WC ($P>0.05$) (Table 2).

Discussion

Conventional percutaneous coronary angiography is the gold standard procedure used to assess the luminal stenosis in CAD [15]. Sixty-four-slice CT systems are now considered the minimum prerequisite for high-quality cardiac and coronary artery imaging, and further developments include systems with two tubes and detectors ('dual source CT') that further improve the image quality beyond conventional multi-slice CT. [16]. In the present study, PAT volume was quantified accu-

rately and reproducibly by dual-source 64-slice CT, and the number and severity of stenotic coronary arteries were determined by percutaneous coronary angiography. Compared with previous studies, results of this study were more reliable and accurate.

Our results showed PAT volume was positively correlated with traditional cardiovascular risk factors, such as BMI, WC, male gender, hypertension, diabetes, age, TC and LDL-C; therefore, PAT volume reflects the clustering effect of multiple cardiovascular risk factors.

Previous studies on non-invasive imaging examinations have shown that CAD patients have more adipose tissues within the pericardium and around arteries compared with patients without CAD, which was consistent with our findings [17-18]. Logistic regression analysis revealed that PAT volume, WC, and BMI were the independent predictors for CAD; however, after adjusting other cardiovascular risk factors, the correlation between PAT volume and CAD was weakened. In addition, ROC analysis indicated PAT volume was better than WC and BMI in predicting CAD, with favorable sensitivity and specificity at a cut-off point of 203.04 cm^3 . Our results indicate that PAT volume should be considered as a novel imaging-based risk factor for CAD; comparable to traditional cardio-metabolic or obesity measures [19].

Previous studies examined the association of PAT volume with CAC and obstructive as well as non-obstructive CAD, but most of them showed either a progressive association [11,20-22], or no association [23-24]. In the present study, the severity of coronary calcification was shown to be proportional to PAT volume and patient age. Percutaneous coronary angiography showed that PAT volume increased with the increase in the number of sclerotic coronary arteries. PAT volume, BMI and FBG were independent risk factors for Gensini score, and PAT volume had the most obvious influence on Gensini score. Thus, PAT volume is positively associated with severity of coronary artery stenosis and may serve as another predictor for the CAD severity. Our results are consistent with recent population-based studies that convincingly linked PAT volume to cardiovascular events [8,19,25].

PAT is metabolically active and is a source of both pro-inflammatory as well as anti-inflammatory cytokines that have both paracrine and systemic effects. Under ischemic conditions, the adipose tissue expands, and becomes hypoxic and dysfunctional [26]. These changes reduce the production of protective adipocytokines, such as adiponectin [27] and cytokine interleukin (IL)-10 [28], but increase that of detrimental adipocytokines, such as leptin, resistin, IL-6, tumor necrosis factor- α , and IL-17 [29]. These molecules can reach the

vessel walls by diffusion or by traveling through adventitial neovascularization, which has significant influence on the formation and development of coronary atherosclerosis. PAT of CAD patients are found to have high nuclear factor-kappa B expression and high c-Jun N-terminal kinase (JNK) activity, high systemic lipopolysaccharides levels and high toll-like receptor (TLR)-2 and TLR-4 expression, indicative of macrophage activation [30]. The mRNA and protein expressions of chemerin are also significantly higher in PAT of Han Chinese patients with CAD [31]. In brief, due to the closeness to coronary vessels, PAT may enhance the systemic atherogenic effects, initiate and accelerate the process of atherosclerosis.

Limitations

There are some limitations in our study. First, this is a cross-sectional study and only associations, but no causality, were evaluated. Second, in the present study, the amount of intra-abdominal visceral fat, which is closely related to adverse cardiovascular events, was not measured by CT. Additional abdominal CT would increase the radiation dose in these patients. Third, this study was conducted in Chinese patients, and generalization to other ethnic groups is uncertain. Finally, markers of inflammation, as well as adipocytokines, were not determined in our study, and these markers may provide support for a causal association between PAT and coronary atherosclerosis.

Conclusion

PAT volume is significantly correlated with traditional cardiovascular risk factors, and may reflect the integrated effect of multiple risk factors in individual patients. PAT volume is an independent predictor for the presence and severity of CAD, and is a more reliable marker for evaluating unfavorable cardiometabolic state and cardiovascular risk stratification, compared with CAC, BMI and WC.

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