Pericardial fat volume is an independent risk factor for the severity of coronary artery disease in patients with preserved ejection fraction

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Introduction

Pericardial fat is a type of visceral adipose tissue (VAT) that is defined as the adipose tissue between the surface of the myocardium and the epicardium. Similar to other VAT, pericardial fat serves an important endocrine and inflammatory function, given its direct apposition to the myocardium and coronary arteries [1,2]. Pericardial fat may play a central role in the pathogenesis of cardiovascular disease, mediated by its inflammatory properties [3].

Kaya et al. [4] reported that an echocardiographic epicardial fat thickness is independently associated with the presence of coronary artery disease (CAD), and Dagyasumberel et al. [5] reported epicardial adipose tissue/body surface area was the single predictor for >50% coronary luminal narrowing in men. Recent studies demonstrated that 64-multi detector computed tomography (MDCT) is suitable for volumetric quantization. However, there have been no reports on the association between the pericardial fat volume (PFV) and the severity of coronary lesions. We, therefore, hypothesized that the pericardial fat increased steeply in patients with significant CAD. In this study, body surface area-indexed PFV (PFV, cm^3/m^2) was measured by MDCT, and the relationship between the PFV and the severity of CAD was evaluated in patients referred for coronary angiography.
Methods

Study population

A total of 105 consecutive ischemic heart disease (IHD) patients who underwent MDCT angiograms and coronary angiography between May 2012 and September 2013 were evaluated. Patients with a history of previous cardiac surgery, percutaneous coronary intervention, symptomatic heart failure, acute coronary syndrome, cardiomyopathy, and severe renal failure were excluded from the study. Written, informed consent was obtained from all patients.

Cardiac computed tomography scan protocol

Cardiac CT scans were performed with MDCT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan) used with parameters as previously reported [6]. Reconstruction sets at 75% of the cardiac cycle or at a particular optimal phase were prepared from the raw data files. The contrast material (Omnipaque-300; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) was administered using a mechanical power injector through a 20-gauge cannula inserted into the antecubital vein. To minimize differences in the arterial enhancement across the patients, a body weight-tailored contrast material dose (0.7 mL/kg) and fixed injection duration (9 s) were used [7]. An oral β-blocker (metoprolol, 20 mg) was administered immediately prior to CT imaging to maintain heart rates at <65 bpm and thus improve image resolution. The reconstructed CT image data were transferred to a workstation for post-processing (ZIO M900, Admin/ZIO, Tokyo, Japan).

Quantification of epicardial fat volume with CT

PFV was measured three-dimensionally in all patients using contrast-enhanced images, as reported previously [7–9]. Segmentation of the overall volume was automatically interpolated using manually defined tracings. Next, PFV was quantified by calculating the total volume of the tissue whose CT density ranged from −190 to −30 Hounsfield units within the pericardial cavity using the workstation (Fig. 1). We trimmed along the pericardial sac using axial, coronal, and sagittal slices, volume-rendered images. PFV was defined as any adipose tissue located within the pericardial sac. A slice 1 cm above the most cranial slice including the left anterior descending coronary artery (LAD) was defined to be the superior border of the pericardial fat. Patients were categorized according to tertiles of PFVi: low-tertile (PFVi < 81.2 cm³/m², n = 35); mid-tertile (81.2 cm³/m² ≤ PFVi ≤ 114 cm³/m², n = 35), and high-tertile (PFVi > 114 cm³/m², n = 35).

Coronary angiography and analysis

Based on the modified AHA classification, the coronary arteries were divided into 17 segments, and the segments with a diameter >2.0 mm were analyzed.

CAD was defined as ≥75% stenosis (according to the American Heart Association classification) on conventional coronary angiography. Conventional coronary angiograms were recorded in multiple projections for the left and the right coronary arteries and reviewed for significant coronary artery obstructions by cardiologists unaware of the amounts of pericardial fat.

The Gensini score (GS), an index of the severity of coronary lesions, was calculated as the sum of all segment scores [10]. Severity scores assigned to the specific percentage luminal diameter reduction of the coronary artery segment were 32 for 100%, 16 for 99%, 8 for 75%, 2 for 50%, and 1 for 25%. Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery 5 ×; the proximal segment of the LAD 2.5 ×; the proximal segment of the circumflex artery 2.5 ×, and the mid-segment of the LAD 1.5 ×.

Assessment of risk factors and covariates

Blood was drawn after an overnight fast. Hypertension was defined as a systolic blood pressure ≥130 mmHg, a diastolic blood pressure ≥85 mmHg, or the use of an antihypertensive treatment. A fasting triglyceride level ≥150 mg/dL and a high-density lipoprotein (HDL) cholesterol level < 40 mg/dL were considered abnormal. Diabetes mellitus was diagnosed based on the criteria set by the World Health Organization or by the use of hypoglycemic agents or insulin. Abdominal obesity was defined as a waist circumference ≥85 cm for Japanese males and ≥90 cm for Japanese females [11]. Metabolic syndrome (MetS) was diagnosed according to the modified Adult Treatment Panel III criteria, which include the waist circumference with the presence of three or more metabolic abnormalities [9].

Statistical analysis

Categorical variables are reported as numbers (%), and continuous variables are reported as mean ± SD. The chi-square test was used for comparing categorical variables, and the unpaired t-test was used for continuous variables. A p-value < 0.05 was considered significant, and all tests were two-tailed. All analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

![Fig. 1. Representative case with high pericardial fat volume of a 49-year-old male with metabolic syndrome with a waist circumference of 106 cm. Invasive coronary angiography shows a significant stenosis at the middle segment of the left anterior descending coronary artery (A, arrow). Angiography with 64-multi detector computed tomography shows a large amount of pericardial fat (B). The parietal pericardium (open arrow), paracardial fat (P), epicardial fat (E), coronary sinus (CS), and esophagus (Eso) are visible. Solid arrows (B), fatty deposits within the atrial septum. And pericardial adipose tissue has been reconstructed three-dimensionally (C). RV, right ventricle; LV, left ventricle.](image-url)
Results

Study sample characteristics

Table 1 lists the clinical characteristics of the study population by tertiles of PFVi. Most patients were men (77%), and the mean age of all patients was 68 ± 10 years. BMI and waist circumference were significantly larger and hypertension was more common in the high-tertile group than in the low-tertile group (p < 0.05). HDL-cholesterol was lower in the high-tertile group than in the low-tertile group (p < 0.05), and the prevalence of MetS was 41%. Fig. 1 shows a representative case of a patient with MetS with a large amount of pericardial fat.

Overall, the mean PFVi was 102 ± 35 (range 35–210) cm²/m². Three-vessel disease was more frequent in the high-tertile group than in the other groups (p < 0.05) (Table 2). GS was significantly different between the high-tertile group and the low-tertile group (p < 0.05), indicating a stepwise decrease in GS from high-tertile to mid-tertile and to low-tertile.

Correlations between PFVi, BMI, and the Gensini score

PFVi correlated positively with BMI (r = 0.376, p = 0.0001; Fig. 2A). GS had a significant positive correlation with PFVi (r = 0.514, p < 0.0001; Fig. 2B). However, no significant association was found between GS and BMI or waist circumference.

Factors associated with the Gensini score

Multiple risk factors have been associated with the severity of CAD, including age, HDL-cholesterol, and PFVi. The results of univariate and multivariate linear regression analyses examining the association between GS and these risk factors are shown in Table 3. On univariate linear regression analysis, multiple risk factors, including age, HDL-cholesterol and PFVi, were significantly related to GS (r = 0.248, r = 0.329, and r = 0.514, respectively, p < 0.05). Multiple regression analysis was performed to identify the independent risk factors associated with the GS. HDL-cholesterol (B = −0.587; 95% CI: −1.049 to −0.126, p = 0.013), and PFVi (B = 0.423; 95% CI: 0.235–0.611, p < 0.001) were the strongest independent variables related to the Gensini score.

Discussion

Major findings

The present study demonstrated the relationship between coronary stenosis and PFVi as measured by MDCT. The major

![Fig. 2](Image)

**Table 1** Baseline characteristics of the study patients by tertiles of indexed pericardial fat volume.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Indexed pericardial fat volume (cm³/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-tertile</td>
</tr>
<tr>
<td>Number</td>
<td>35</td>
</tr>
<tr>
<td>Age</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>Male/female</td>
<td>27/8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.0 ± 2.6</td>
</tr>
<tr>
<td>Waist circumferences (cm)</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>22 (64)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>28 (82)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>113 ± 25</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>144 ± 48</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>119 ± 27</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.5 ± 1.2</td>
</tr>
<tr>
<td>Metabolic syndrome (Adult Treatment Panel III) (%)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>19 (57)</td>
</tr>
<tr>
<td>Medications</td>
<td>Statins (%)</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors or ARBs (%)</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction on echocardiography, %</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD, number of patients (%). LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. * p < 0.05 compared to the low-tertile group.

**Table 2** Comparison of MDCT and coronary angiography results for patients by tertiles of indexed pericardial fat volume.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PFVi (cm³/m²)</th>
<th>Low-tertile</th>
<th>Mid-tertile</th>
<th>High-tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFV (cm³)</td>
<td>114 ± 16</td>
<td>159 ± 22</td>
<td>243 ± 47</td>
<td></td>
</tr>
<tr>
<td>PFVi (cm³/m²)</td>
<td>68 ± 9</td>
<td>97 ± 8</td>
<td>144 ± 26</td>
<td></td>
</tr>
</tbody>
</table>

Coronary stenosis (≥75% diameter reduction)

1-Vessel disease, n (%) | 20 (57) | 23 (68) | 14 (41) |
2-Vessel disease, n (%) | 9 (25) | 6 (17) | 10 (28) |
3-Vessel disease, n (%) | 6 (17) | 5 (14) | 11 (31) |

Gensini score | 28 ± 23 | 32 ± 28 | 54 ± 34 |

Data are presented as means ± SD, number of patients (%). MDCT, 64-multi detector computed tomography; PFV, pericardial fat volume; PFVi, indexed pericardial fat volume. * p < 0.05 compared to the low-tertile group.
findings of the study were as follows. First, consistent with most previous observations [4,6], it was demonstrated that accumulation of PFVi was related to increased severity of CAD in patients with preserved ejection fraction. Second, PFVi was positively correlated with BMI and was increased in CAD subjects. Third, it was found that the coronary severity score may not be correlated with BMI and waist circumference. This result may be affected by the fact that the number of obese patients was small, and the degree of obesity of most patients in this study was not severe. Finally, high PFVi was the independent predictor of the severity of coronary disease, but markers of visceral adiposity (BMI and waist circumference) were not. Of interest, PFVi remained a significant predictor, suggesting that PFVi is not purely a reflection of VAT in the predisposition to atherosclerosis. The present study is the first to find that accumulation of PFVi was related to increased severity of significant atherosclerotic disease in symptomatic CAD subjects.

### Role of pericardial fat in the pathophysiology

Pericardial adipose tissue is recognized as ectopic fat depot in close proximity to the myocardium and coronary arteries, and it is suspected to be implicated in the pathogenesis of coronary atherosclerosis. It has been hypothesized that, unlike large fat deposits, such as visceral abdominal fat, which primarily act systemically, pericardial fat probably acts locally through mechano-structural or paracrine mechanisms. Several studies have reported the potential role of epicardial fat in the pathophysiology of coronary atherosclerosis [1,2,7], and hypothetical mechanisms of epicardial fat in coronary atherosclerosis have been proposed [12], such as an endocrine effect through adventitial vasa vasorum. Just like coronary arteries, coronary veins are also surrounded by pericardial fat. Therefore, pericardial fat surrounding the thin-walled coronary veins may exert greater systemic effects by diffusion of its small, metabolically active molecules into the circulation. There may also be a direct paracrine effect. Adipokines can diffuse in the interstitial fluid across the vascular wall and stimulate atherogenesis. Pericardial fat is a metabolically active fat depot that is in anatomic proximity to the myocardium, sharing the same microcirculation, and may have important paracrine effects.

In addition, Konishi et al. [7] have shown that pericardial fat had significantly more leukocyte common antigen-positive cells in CAD autopsy cases. Hirata et al. [1] reported that coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. Although the exact pathophysiologic mechanism has not been characterized, it has been hypothesized that pericardial fat releases pro-atherogenic inflammatory cytokines in close proximity to the coronary arteries [3]. Hirata et al. [2] suggested that chronic inflammation in epicardial fat may influence the pathogenesis of coronary atherosclerosis by inflammatory cell infiltration in patients with CAD. Recent reports by other investigators have suggested that epicardial fat may act as a paracrine organ that affects the coronary arteries by promoting chronic inflammation [13] and endothelial dysfunction.

Atherosclerotic plaque formation involves a cascade of events, initiated by endothelial dysfunction, followed by inflammatory cell infiltration into the intima, transcytosis of cholesterol-rich lipoproteins, oxidative modification, foam cell formation, and smooth muscle cell proliferation.

### Pericardial fat as a predictor of CAD

Previous studies have demonstrated that pericardial fat could mediate the development of CAD. It has been found that pericardial fat could contribute to coronary atherosclerosis, myocardial ischemia [14], coronary plaque characteristics [12], and future cardiovascular events [15]. In the present study, PFVi was related to the presence, extension, and stenosis severity of coronary plaque. These findings are in good agreement with a recent report by Mahabadi et al. [16], who found that epicardial fat is associated with coronary events in the general population independent of cardiovascular risk factors.

Furthermore, the PFVi was comparable among patients with stenotic and non-stenotic plaques, suggesting that the accumulation of pericardial fat is associated with early stages of coronary atherosclerosis. Pericardial adipose tissue plays a crucial role in the development of CAD and atherosclerosis, beyond systemic obesity. In this study, PFVi was found to be independently associated with CAD severity, even though it is a small amount of body fat. These findings suggest that pericardial fat is more highly associated with the early development of CAD than simple anthropometric measures of abdominal obesity.

Hence, PFVi measurement may provide novel, additional risk stratification for patients suspected of having CAD, as well as visceral adipose tissue [17]. Together, these results suggest that an increased PFVi may serve as a marker for severe atherosclerosis and might also be a risk factor for significant CAD in the general population. Furthermore, PFVi assessment could contribute to the prevention and management of CAD in patients with preserved ejection fraction. The present finding that the association of PFVi with coronary atherosclerosis was not completely explained by standard risk factors is consistent with the evidence suggesting that the link between PFVi and obesity-related complications may involve novel biological pathways.

### Study limitations

The present study has several limitations. First, we did not have data on visceral fat measurements, which could have influenced the incident CAD [17]. Instead, we used BMI and waist circumference as surrogate markers of visceral adiposity, and the inclusion of these markers in the multivariate model did not attenuate the association of PFVi with the severity of CAD.

Second, data were obtained in routine medical care. Therefore, we could not measure serum or tissue inflammatory cytokines and adipokines, both of which can lead to accelerated atherosclerosis or plaque vulnerability. However, our main aim was to investigate the relationship between the PFVi and the severity of CAD.
Third, our study was a single-center design and the inclusion of self-referred patients may have harbored an inherent bias. Finally, no follow-up data were available. Indeed, whether PFVi quantity may have a prognostic value needs to be evaluated in prospective follow-up studies.

Conclusions

This study demonstrated a significant association between the severity of CAD and PFVi, but not with waist circumference or BMI. Importantly, PFVi with preserved ejection fraction might be more highly associated with the progression of IHD. Therefore, PFVi measurement may be viewed as an indicator of global atherogenic risk.

Acknowledgment

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References