Relationship of epicardial adipose tissue by echocardiography to coronary artery disease


ABSTRACT
Objective: To study the relationship of echocardiographic epicardial adipose tissue (EAT) with coronary artery disease (CAD) risk factors and the extent of coronary atherosclerosis.

Methods: EAT thickness was measured in 527 patients undergoing their first coronary angiography. EAT was defined as an echo-lucent area on the free wall of the right ventricle on the still image of the two-dimensional echocardiogram at end diastole in the parasternal long-axis and parasternal short-axis views. A CT scan at the umbilicus was acquired to measure abdominal visceral adipose tissue (VAT) from a random sample of 30 patients. The extent of coronary atherosclerosis was assessed using a coronary atherosclerosis score based on the quantitative coronary angiography results.

Results: EAT thickness was correlated with abdominal VAT \( r_s = 0.626, p < 0.001 \), age \( r_s = 0.480, p < 0.001 \), waist circumference \( r_s = 0.309, p < 0.001 \), body mass index \( r_s = 0.233, p < 0.001 \), C reactive protein \( r_s = 0.224, p < 0.001 \), and the homeostasis model assessment score \( r_s = 0.249, p < 0.001 \). EAT was thicker in subjects with CAD than in those without CAD (4.0 vs 1.5 mm, \( p < 0.001 \)). Patients with unstable angina had thicker EAT than those with stable angina or atypical chest pain (4.0, 3.0, and 1.5 mm, respectively, \( p < 0.001 \)). EAT \( > 3.0 \) mm was an independent factor of CAD on multiple logistic analysis (odds ratio = 3.357; 95% CI 2.177 to 5.175, \( p < 0.001 \)).

Conclusions: These results suggest that EAT may reflect the amount of visceral fat, which is associated with insulin resistance and inflammation. The echocardiographic measurement of EAT may provide additional information for assessing CAD risk and predicting the extent and activity of CAD.

It is increasingly evident that visceral adipose tissue (VAT) plays a leading part in the development of the metabolic syndrome (MS) and that it is an important coronary artery disease (CAD) risk factor.\(^1\)\(^3\) Waist circumference and imaging modalities, such as abdominal computed tomography (CT) and magnetic resonance imaging (MRI), have been used to estimate VAT.\(^4\)\(^5\) Recently, it was reported that epicardial adipose tissue (EAT) measured by transthoracic echocardiography in obese subjects was well correlated with abdominal VAT assessed by MRI and that echocardiographic EAT could be used as a reliable imaging indicator of VAT.\(^6\) However, to date, the clinical significance of EAT, which is observed during transthoracic echocardiographic examination done as part of a CAD investigation, has not been studied in patients with angina. Therefore, we determined whether echocardiographic EAT reflects VAT in subjects presenting with angina. We also investigated the relationship of EAT to CAD risk factors, MS, the extent of angiographic CAD, and disease activity.

PATIENTS AND METHODS

Patient population
EAT thickness was measured consecutively and prospectively in 527 patients (mean (SD) age 58 (11) years, 267 male) undergoing their first coronary angiography owing to chest pain between January 2005 and October 2005 in our hospital. Patients were excluded from the study if they had any of the following: active inflammation or inflammatory disease, chronic kidney disease, a history of prior revascularisation, heart failure, cardiomyopathy and acute myocardial infarction. Ambiguous cases with possible pericardial effusion were also excluded. Anthropometric measures, such as body mass index and waist and hip circumferences were collected. Plasma lipid profiles, C reactive protein, fibrinogen, uric acid and cardiac enzymes were measured. The homeostasis model assessment (HOMA) score, which reflects insulin resistance, was calculated in non-diabetic patients using fasting plasma insulin and glucose concentrations as previously described.\(^7\) Patients with more than three of five criteria based on the updated ATP guideline were considered to have the MS. Central obesity was considered to be present if the waist circumference was \( > 90 \) cm in men and \( > 80 \) cm in women, which are the threshold values for the Asian population.\(^3\) The MS score was defined as the number of MS components present. The study protocol was approved by our institutional review board, and all patients gave their written informed consent.

Measurement of echocardiographic epicardial adipose tissue
Two-dimensional transthoracic echocardiography (Sequoia C256 with 2.5 MHz transducer; Siemens, Mountain View, California, USA) was performed. Recordings of six cycles of the two-dimensional parasternal long-axis view and the parasternal short-axis view at the basal left ventricular level were obtained. We increased the depth of each view until the aortic and mitral valves were positioned lowest on the screen to allow for better visualisation and accurate estimation of EAT. EAT was measured on the free wall of the right ventricle in the still images of the two-dimensional echocardiogram obtained at end diastole on both...
parasternal long-axis and short-axis views (fig 1). The anterior echo-lucent space between the linear echo-dense parietal pericardium and the right ventricular epicardium was considered to be EAT. Mediastinal fat, seen as an echo-lucent area located above the parietal pericardium, was not included in the EAT measurement. The average value of two images obtained in the parasternal long-axis and short-axis views was calculated.

**Measurement of abdominal visceral adipose tissue**
A random sample of 30 patients had CT scans using a GE Highspeed Advantage (GE Medical System, Milwaukee, USA) according to our hospital’s protocol. All scans were performed in the supine position using a slice diameter of 40 cm with a thickness of 3 mm. The images were generated with a 200 mA, 120–140 kV beam for a duration of a second. Scans were displayed in a matrix of 512×512 picture elements. We selected a sequence of five images obtained at 3 mm intervals. The central image of the sequence was located at the umbilicus; two images were above and two images were below this level. On each CT image, the intra-abdominal cavity was outlined by tracing the transverse fascia excluding the vertebral body. The CT attenuation score for fat ranged from −50 to −250. After three-dimensional reconstruction of the images, abdominal VAT volumes were calculated using histogram-based volume analysis.

**Coronary angiography**
Quantitative coronary angiographic analysis (Quanctcor QCA, version 4.0; Pie Medical Imaging, Maastricht, The Netherlands)

**Table 1**  Baseline characteristics according to the thickness of epicardial adipose tissue (EAT) (n = 527)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EAT &lt;3.0 mm (n = 263)</th>
<th>EAT &gt;3.0 mm (n = 264)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>54 (11)</td>
<td>63 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, No (%)</td>
<td>138 (52)</td>
<td>129 (49)</td>
<td>0.407</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>24.7 (3.2)</td>
<td>25.7 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm), mean (SD)</td>
<td>87.6 (9.8)</td>
<td>92.0 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, No (%)</td>
<td>119 (45)</td>
<td>173 (66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, No (%)</td>
<td>50 (19)</td>
<td>75 (28)</td>
<td>0.011</td>
</tr>
<tr>
<td>Smoking, No (%)</td>
<td>94 (36)</td>
<td>82 (31)</td>
<td>0.255</td>
</tr>
<tr>
<td>Metabolic syndrome, No (%)</td>
<td>131 (50)</td>
<td>196 (74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiographic CAD, No (%)</td>
<td>79 (30)</td>
<td>181 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable angina, No (%)</td>
<td>60 (23)</td>
<td>152 (58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l), mean (SD)</td>
<td>4.42 (0.88)</td>
<td>4.55 (1.01)</td>
<td>0.072</td>
</tr>
<tr>
<td>Triglyceride (mmol/l), mean (SD)</td>
<td>1.66 (1.02)</td>
<td>1.76 (1.06)</td>
<td>0.248</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l), mean (SD)</td>
<td>1.22 (0.34)</td>
<td>1.14 (0.26)</td>
<td>0.028</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l), mean (SD)</td>
<td>2.46 (0.75)</td>
<td>2.66 (0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td>C reactive protein (mg/l), mean (SD)</td>
<td>2.0 (4.0)</td>
<td>2.9 (5.2)</td>
<td>0.040</td>
</tr>
<tr>
<td>HOMA score, mean (SD)*</td>
<td>2.2 (1.9)</td>
<td>2.8 (2.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Uric acid (µmol/l), mean (SD)</td>
<td>303 (95)</td>
<td>321 (178)</td>
<td>0.135</td>
</tr>
<tr>
<td>Fibrinogen (g/l), mean (SD)</td>
<td>3.4 (0.9)</td>
<td>3.7 (1.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*The homeostasis model assessment (HOMA) score was calculated only in non-diabetic patients (n = 402).
CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
was performed by one single experienced technician who was unaware of the patients’ clinical information. On quantitative analysis of the coronary angiograms, the presence of one or more stenoses $\geq 50\%$ in diameter of a major epicardial vessel was considered to be significant CAD. The extent of CAD was quantified using the number of vessels with $\geq 50\%$ stenosis and a coronary atherosclerosis score as follows.\(^8\) The coronary artery tree was divided into nine segments: the left main coronary artery, the proximal, mid-, and distal left anterior descending artery, the proximal circumflex artery including the first obtuse marginal branch, the circumflex artery distal to the first marginal branch, the proximal and mid-right coronary artery, and the posterior descending artery. Each of these segments was scored from 0 to 3 depending on the most severe stenosis using the following system: 0 = normal, 1 = stenosis between 1% and 49%, 2 = stenosis between 50% and 99%, and 3 = total occlusion. A coronary atherosclerosis score was generated as the sum of the scores in all segments.

**Statistics**

SPSS version 12.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. All continuous variables are expressed as mean (SD); categorical variables are expressed as number and percentage. We compared the characteristics of patients who had $\leq 3.0$ mm of EAT with those who had $\geq 3.0$ mm of EAT. Comparisons of continuous variables were performed using the unpaired Student t test. Analyses of discrete variables were performed using $\chi^2$ tests. Owing to its skewed distribution, the significance of any differences between groups in the median values of EAT thickness were evaluated using the Wilcoxon rank-sum test. Comparison of EAT thickness according to the MS score, the number of vessels with $\geq 50\%$ narrowing, and the clinical presentation was done using the Kruskal–Wallis test. Correlations of EAT with various clinical and biochemical variables, including abdominal VAT, were examined by Spearman correlation analysis. A set of well-recognised CAD risk factors were included in a logistic regression model of angiographic CAD.\(^1\)\(^9\) EAT thickness was then added to this model to determine whether there was any additional prognostic value. A receiver operating characteristic curve analysis was used to assess the discrimination of CAD based on well-known CAD risk factors and EAT thickness. One-sample paired t test was performed to evaluate inter- and intraobserver variability in the measurement of EAT from 30 randomly selected subjects. Variability was expressed as mean (SD) of the absolute difference between the two sets of measurements.

**RESULTS**

**Clinical characteristics**

Table 1 lists patients’ detailed clinical characteristics according to the thickness of EAT. Our study group consisted of 527 patients (267 men) with a mean (SD) age of 58 (11) years. The MS criteria were fulfilled in 327 patients. There were 125 diabetic patients and 212 patients who presented with unstable angina. On coronary angiography, significant CAD was detected in 260 patients. The patients who had $\geq 3.0$ mm of EAT were older and had higher body mass index and greater waist circumference than those who had $<3.0$ mm of EAT. Additionally, there were more prevalent hypertension, diabetes, MS, angiographic CAD, and unstable angina, and the level of low-density lipoprotein cholesterol, C reactive protein, HOMA score, uric acid, and fibrinogen was higher. Additionally, the level of high-density lipoprotein cholesterol was lower in patients who had $\geq 3.0$ mm of EAT compared with those who had $<3.0$ mm of EAT.

**Epicardial adipose tissue thickness**

The frequency histogram of EAT thickness was skewed to the left (fig 2). EAT thickness ranged from 0 through 12 mm. The frequency histogram of EAT thickness was skewed to the left (fig 2). EAT thickness ranged from 0 through 12 mm. The frequency histogram of EAT thickness was skewed to the left (fig 2). EAT thickness ranged from 0 through 12 mm. The frequency histogram of EAT thickness was skewed to the left (fig 2). EAT thickness ranged from 0 through 12 mm. The frequency histogram of EAT thickness was skewed to the left (fig 2). EAT thickness ranged from 0 through 12 mm.
Coronary artery disease

Table 3  Multiple logistic analysis of coronary artery disease risk factors (n = 527)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.775 (1.931 to 6.254)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male ≥45 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female ≥55 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.801 (1.142 to 2.842)</td>
<td>0.011</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.842 (1.200 to 2.826)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.555 (1.544 to 4.227)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C reactive protein ≥1 mg/l</td>
<td>1.696 (1.117 to 2.576)</td>
<td>0.013</td>
</tr>
<tr>
<td>Epicardial adipose tissue ≥3 mm</td>
<td>3.357 (2.177 to 5.175)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Comparison of the thickness of epicardial adipose tissue according to the number of components of the metabolic syndrome

The median EAT thickness was greater in patients with unstable angina than in those with stable angina or atypical chest pain (unstable angina, 4 vs stable angina, 3 vs atypical chest pain, 1.5 mm, respectively, p < 0.001, fig 4B). EAT was thicker in patients with significant CAD than in those without CAD (4.0 vs 1.5 mm, p < 0.001). Patients with multi-vessel CAD had significantly thicker EAT than those with single-vessel disease and normal coronary arteries or minimal CAD (multivessel CAD, 4 vs single-vessel disease, 3.5 vs normal or minimal CAD, 1.5 mm, respectively, p < 0.001, fig 4B). The median EAT thickness was greater in patients with unstable angina than in those with stable angina or atypical chest pain (unstable angina, 4 vs stable angina, 3 vs atypical chest pain, 1.5 mm, respectively, p < 0.001, fig 4C).

Comparison of the thickness of epicardial adipose tissue according to the presence of coronary artery disease, the extent of coronary artery disease, and the clinical presentation

EAT was thicker in patients with significant CAD than in those without CAD (4.0 vs 1.5 mm, p < 0.001). Patients with multi-vessel CAD had significantly thicker EAT than those with single-vessel disease and normal coronary arteries or minimal CAD (multivessel CAD, 4 vs single-vessel disease, 3.5 vs normal or minimal CAD, 1.5 mm, respectively, p < 0.001, fig 4B). The median EAT thickness was greater in patients with unstable angina than in those with stable angina or atypical chest pain (unstable angina, 4 vs stable angina, 3 vs atypical chest pain, 1.5 mm, respectively, p < 0.001, fig 4C).

Epicardial adipose tissue as a predictor of coronary artery disease

Table 3 shows the multiple logistic analysis of the CAD risk factors. In addition to the well-known CAD risk factors, such as age, smoking, hypertension, C reactive protein, and diabetes, epicardial adipose tissue was an independent factor associated with angiographic CAD in this study population. The receiver operating characteristic curve using the predicted probability from the logistic regression model in table 3 excluding EAT yielded an area under the curve of 0.739 (95% CI 0.695 to 0.783, p < 0.001). When EAT thickness was added to the CAD risk factors, the area under the curve improved to 0.783 (95% CI 0.742 to 0.824, p < 0.001, fig 5).

DISCUSSION

The present study demonstrated that echocardiographic EAT could be used as another imaging indicator of VAT and that EAT was related to various CAD risk factors, MS, and the severity of angiographic CAD. Although the presence of epicardial fat has been discussed in previous autopsy studies, its clinical significance and function have not been extensively studied. It has been suggested that EAT may act as a local energy supply for the adjacent myocardium or act as a buffer against toxic levels of free fatty acids, or both. EAT was also proposed as a source of several inflammatory mediators, given that EAT had higher levels of inflammatory markers than subcutaneous adipose tissue in patients undergoing coronary artery bypass surgery. As far as we know, our paper is the first study to have evaluated the clinical significance of EAT measured by echocardiography in patients presenting with angina.
measured by CT scan. Insulin resistance has been known to be EAT thickness has a good correlation with abdominal VAT as they are expensive. Recently, echocardiographic EAT assess- CT scan and MRI are certainly more precise and reliable, but neous and visceral fat. Imaging techniques such as abdominal mass. However, it often cannot discriminate between subcuta- neous and visceral fat. Imaging techniques such as abdominal CT scan and MRI are certainly more precise and reliable, but they are expensive. Recently, echocardiographic EAT assessment has been proposed as a new imaging indicator of VAT, since it has a good correlation with abdominal VAT measured by MRI. The present study confirms that echocardiographic EAT thickness has a good correlation with abdominal VAT as measured by CT scan. Insulin resistance has been known to be an important factor in the pathogenesis of MS. In the present study, the HOMA score, which represents insulin resistance, was weakly correlated with EAT thickness. These results are consistent with an earlier study that reported that EAT was significantly related to obesity-related insulin resistance. Patients with MS had thicker EAT than those without MS, and EAT thickness increased linearly with an increase in the number of MS components. These results suggest that echocardiographic EAT thickness might be used as another imaging indicator of VAT, which is known to be related to insulin resistance and has a key role in the development of MS.

Relationship to the extent of coronary artery disease
Several studies have shown that increased abdominal VAT is associated with CAD. We investigated the relationship between EAT thickness and the extent of coronary atherosclerosis. The subjects with angiographically significant CAD had thicker EAT than those without CAD. There was a moderate correlation between the thickness of EAT and the coronary atherosclerosis score. EAT thickness increased as the number of vessels with ≥50% stenosis increased. On multiple logistic analysis of various CAD risk factors, EAT was an independent factor associated with CAD. These results are consistent with an earlier study that demonstrated that pericardial fat volume measured on CT scan was an independent variable for the presence of angiographic CAD in Japanese men. Thus, EAT may be considered to be an independent factor associated with CAD that can be used to predict the extent of coronary atherosclerosis.

Relationship to coronary artery disease activity
It has been reported that human EAT has a high concentration of inflammatory mediators, such as tumour necrosis factor, monocyte chemotactic protein-1, interleukin 1β, interleukin 6, and interleukin 6 soluble receptors, and that it expresses a pathogenic profile of adipokines in patients undergoing coronary artery bypass graft surgery; this suggests that EAT is a site of active inflammation. We demonstrated a statistically significant correlation between EAT thickness and the C reactive protein level, though the degree of correlation was weak. The median EAT thickness was higher in subjects with unstable angina than in those with atypical chest pain or stable angina. These findings suggest that EAT may serve as a source of inflammation that can influence CAD activity.

Echocardiographic method for the measurement of epicardial adipose tissue
We selected an area above the right ventricular free wall on the parasternal view to measure EAT thickness, as described previously. Autopsy studies have reported that this area has a somewhat higher EAT layer thickness. The parasternal views, which are the routinely obtained standard images during transthoracic echocardiography, allow the simple measurement of EAT thickness on the right ventricle with good reproducibility. The median EAT thickness was lower in our study cohort than in the previous study population. This disagreement may be due to different study cohorts. Our study population was Asian and had a lower body mass index, whereas the previous study population was performed in obese Caucasian subjects. The echo-lucent area between the parietal pericardium and the right ventricular epicardium was considered to be EAT. Although massive pericardial fat could be misdiagnosed as pericardial effusion, in most patients we could differentiate pericardial effusion from epicardial fat using M-mode echocardiography. Pericardial effusion was delineated as a more homogeneous echo-free space with clear visualisation of both pericardial layers on M-mode echocardiography. In contrast, compared with pericardial effusion, EAT presented as a somewhat inhomogeneous, whitish-speckled, echo-lucent area. Patients in whom it was difficult to differentiate epicardial fat from a pericardial effusion were excluded from the study.

Limitations
The present study has several limitations. First, the study group was highly selected, since it involved only Asian patients undergoing their first coronary angiography due to chest pain. As well, the design of our study was cross-sectional. A prospective cohort study might be necessary to elucidate the clinical significance of EAT in the general population. Second, EAT thickness on the right ventricular free wall does not exactly represent the amount of total epicardial fat. In some subjects, there is also abundant epicardial fat on the left ventricular apex. However, previous studies have shown that there is a good correlation between EAT thickness on echocardiography and on MRI; thus, echocardiography appears to be an accurate method to estimate EAT thickness. One can assume that EAT thickness on the right ventricular free wall assesses the total amount of epicardial fat, since this area is known to have the highest epicardial fat layer, and EAT thickness on the right ventricular free wall was well correlated with abdominal VAT both in the present study and in a previous study. Third, the coronary atherosclerosis score does not represent the actual atheroma volume or plaque burden; it is a crude method for evaluation of inflammatory mediators, such as tumour necrosis factor, monocyte chemotactic protein-1, interleukin 1β, interleukin 6, and interleukin 6 soluble receptors, and that it expresses a pathogenic profile of adipokines in patients undergoing coronary artery bypass graft surgery; this suggests that EAT is a site of active inflammation.
Coronary artery disease estimating CAD severity. However, coronary angiography is the most widely used technique for assessing coronary anatomy, and this score was validated in a previous study that compared C reactive protein with the extent of CAD.³

CONCLUSION
In conclusion, measuring EAT thickness using transthoracic echocardiography is both simple and feasible. The present study results indicate that EAT may reflect the amount of visceral fat, which is related to insulin resistance and inflammation. The echocardiographic measurement of EAT may provide additional information for estimating CAD risk, diagnosing the MS, and predicting the presence of coronary atherosclerosis.

Acknowledgements: We are indebted to Dr Seung-Soo Sheen for his statistical assistance.

Funding: Supported by a grant from the Korean Society of Echocardiography.

Competing interests: None declared.

Ethics approval: Obtained.

REFERENCES
Relationship of epicardial adipose tissue by echocardiography to coronary artery disease


*Heart* 2008 94: e7 originally published online October 8, 2007
doi: 10.1136/hrt.2007.118471

Updated information and services can be found at:
http://heart.bmj.com/content/94/3/e7.full.html

**References**

This article cites 19 articles, 8 of which can be accessed free at:
http://heart.bmj.com/content/94/3/e7.full.html#ref-list-1

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/