A single slice measure of epicardial adipose tissue can serve as an indirect measure of total epicardial adipose tissue burden and is associated with obstructive coronary artery disease

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Aims
To evaluate the practical use of the single slice measurement of epicardial adipose tissue (EAT) at the level of the left main coronary artery (EATLM) in predicting the presence of obstructive coronary artery disease (CAD).

Methods and results
Quantification of EATTotal and EATLM was performed on non-contrast CT scans of consecutive patients (without history of revascularization, cardiac transplantation, device implantation, and congenital heart disease) who underwent coronary artery calcium (CAC) scoring and computed tomographic coronary angiography (CTA) between May 2011 and July 2011. One hundred and ninety-two patients were evaluated, of which 47 had obstructive CAD (≥50% stenosis). EATLM (3.8 ± 2.2 cm³) and EATTotal (126.2 ± 56.3 cm³) are highly correlated (r = 0.89, P < 0.001). Multivariate analysis revealed that both EATLM (OR: 1.204 per 1 cm³, 95% CI: 1.028–1.411, P = 0.021) and EATTotal (OR: 1.007 per 10 cm³, 95% CI: 1.000–1.013, P = 0.038) are associated with obstructive CAD. However, when the CAC score was added to multivariate analysis, both failed to show statistical significance. (EATTotal, OR 1.004 per 1 cm³, 95% CI: 0.996–1.011, P = 0.328 and EATLM, OR: 1.136 per 10 cm³, 95% CI: 0.948–1.362) ROC curve analysis revealed that both EATTotal and EATLM are of incremental value in detecting CAD, when compared with traditional risk scores (NCEP plus EATTotal plus BMI and NCEP plus EATLM plus BMI vs. NCEP alone; AUC 0.7090, P = 0.009 and 0.7167, P = 0.003 vs. 0.6069, respectively).

Conclusion
Measuring epicardial adipose tissue on a single slice at the level of the left main coronary artery may serve as an indirect measure of total epicardial adipose tissue burden. EATLM and EATTotal are independently associated with obstructive coronary artery disease and are incremental to traditional risk factors for predicting its presence.

Keywords
Computed tomography • Coronary angiography • Epicardial adipose tissue • Coronary artery disease

Introduction
Epicardial adipose tissue (EAT), located between the visceral pericardium and myocardium, possesses unique metabolic and paracrine properties which have implicated it in the development and progression of coronary artery disease (CAD).¹⁻³ Recent data support the association between EAT burden and markers of coronary artery calcium (CAC) score and coronary atherosclerotic burden.⁴⁻⁸

CT-based characterization of EAT is emerging as an active area of investigation, however, discrepancies exist between methodologies used to quantify EAT suggesting that there is a need for standardization.⁹⁻¹⁰ Also needed is a simple streamlined approach, whereby the clinical reader is able to assess EAT in a time-efficient manner. Though it may be desirable to quantify the total volume of EAT (EATTotal) on consecutive slices acquired with complete cardiac coverage, previous work done by Oyama et al.⁹ identified the adipose tissue at the level of the left main coronary artery to be best correlated with EATTotal. The relationship between EAT identified on a single slice and the presence of obstructive CAD remains unproven.

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The objective of this study was to determine whether EAT assessed on a single axial CT slice at the level of left main coronary artery (EATLM) correlates with EATTotal and with obstructive CAD, and if EATLM has incremental value over traditional cardiac risk factors.

**Methods**

**Patient selection**
Consecutive patients presenting for coronary CT angiography (CCTA) between May 2011 and July 2011 were retrospectively screened and included if both CAC and CCTA were performed. Patients were excluded if they had prior revascularization, congenital heart disease, heart transplant, device implantation, and valvular surgery. These patients were excluded since the pericardial fat has been disturbed and artefacts on the images makes the measurement of adipose tissue more challenging. This study was approved by the local institutional research ethics board.

**Cardiac CT**
Prior to imaging, metoprolol or diltiazem was administered in order to achieve a heart rate of \( \leq 65 \) bpm and nitroglycerin (0.8 mg) was administered sublingually.10 – 12 Scans were performed with a GE VCT (GE Healthcare, Milwaukee, WI, USA).

For CAC, a non-contrast enhanced, prospective ECG-triggered image acquisition (collimation = 64 \( \times 0.625 \) mm; gantry rotation = 350 ms; tube current = 400 – 800 mA; tube voltage = 120 kV) was performed at the 70% phase and images were reconstructed using a slice thickness of 2.5 mm. Agatston scores were measured by two experienced observers blinded to clinical data.13

For CCTA, contrast enhanced prospective ECG-triggered images were acquired (tube current = 400 – 800 mA; tube voltage = 100 or 120 kV) using a triphasic contrast administration protocol.12,14 Reconstructions of the CCTA data sets were done with a slice thickness of 0.625 mm at the 70, 75, and 80% phases.14

**EATTotal**
Quantification of EATTotal was performed semi-automatically on CAC scans using a TeraRecon Aquarius Workstation (version 4.4.7, TeraRecon, Inc., San Mateo, CA, USA). The pericardial border of every fourth axial slice was manually traced with automated tracing between the manual measures. All borders were subsequently reviewed and manually adjusted to ensure accuracy. The superior and inferior limits were defined as the lowest visible portion of the bifurcation of pulmonary artery and the lowest slice containing diaphragmatic pericardium, respectively. EATTotal was then calculated as the total volume of EAT between these limits with an attenuation of \(-250 \) to \(-30 \) Hounsfield units (HU) (Figure 1).4,7

**EATLM**
Using the same attenuation threshold, EATLM was manually quantified on a single non-contrast enhanced axial 2.5 mm slice at the level of the ostium of the left main coronary artery (Figure 2).

**Clinical predictors**
Pre-test probability for obstructive CAD was assessed using the National Cholesterol Education Program (NCEP)/Adult Treatment Panel III cardiac risk score.12,15 The NCEP score is used in clinical practice to calculate a patient’s 10-year risk of having a cardiac event based on age, gender, total cholesterol, HDL cholesterol, smoking status, and presence or treatment of hypertension.

**Statistical analysis**
Statistical analyses were performed using SAS (version 9.1.3, SAS Institute, Inc., Cary, NC, USA) and SPSS (version 21, SPSS, Inc., Chicago, IL, USA). Images were post-processed using a GE Advantage Volume Share Workstation (GE Healthcare, Milwaukee, WI, USA). A 17-segment model of the coronary system and 4-point grading score [normal, mild (<50%), moderate (50–69%), and severe (≥70%)] was used in evaluating the degree of stenosis.17 For this study, patients presenting with at least one lesion with ≥50% stenosis were considered to have obstructive CAD.

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**Figure 1** Measurement of EATLM. EATLM was measured by manually tracing the pericardial outline at the level of the ostium of the left main coronary artery. The volume of tissue within the outlined boundary with an attenuation of \(-250 \) to \(-30 \) HU was calculated. The image to the right represents the EATLM within the region of interest (red line).
USA). Continuous variables are presented as means and standard deviations, and categorical variables are presented as percentages with frequencies. Using a one-sample Kolmogorov-Smirnov test, the normal distribution of data was tested. A Pearson’s correlation coefficient was calculated to assess the relationship between EATLM and EATTotal. Step-wise multivariate logistic regression model was performed where traditional risk factors were entered into the initial step of the model, followed by either EATLM or EATTotal. Factors with a \( P \leq 0.05 \) on univariate analysis were entered into the multivariate model. The two-sided Wilcoxon rank sum test and the two-sided \( \chi^2 \) test were used to compare continuous and categorical variables, respectively. Statistical significance was defined as a \( P \)-value of \( < 0.05 \). ROC curve analysis was used to determine the incremental value of EATLM and EATTotal over body mass index (BMI), NCEP, and pre-test probability of obstructive CAD. A random subset of 25 patients was selected to evaluate reproducibility of EATLM. Both inter-observer and intra-observer reproducibility were assessed by the use of the intra-class correlation coefficient (ICC). A single expert reader repeated the measurement of the EATLM 1 year after the original measurement. Inter-observer reproducibility was assessed using measurements obtained by two-independent expert readers.

**Results**

**Patient characteristics**

One hundred and ninety-two consecutive patients [101 (52.6%) men, mean age = 55 ± 10 years] meeting study criteria were, retrospectively, identified between May 2011 and July 2011 (Table 1). Indications for cardiac CT were as follows: chest pain [121 (63.0%)], dyspnoea [34 (17.7%)], significant risk factors for CAD [17 (8.9%)], palpitations [7 (3.6%)], and other [13 (3.8%)].

**Quantification of epicardial adipose tissue:**

**EATLM and EATTotal**

The mean EATTotal was 126.2 ± 56.3 cm³, whereas mean EATLM was 3.8 ± 2.2 cm³ and both measures are highly correlated \((r = 0.89, P < 0.001)\) (Figure 3). The time duration required to measure EATLM and EATTotal range from 15–20 s and 8–10 min, respectively. A total of 47 (24.5%) patients were found to have obstructive CAD (Table 1). Univariate analysis was performed to assess the
relationship between traditional cardiac risk factors, CAC score, EATLM, and EATTotal with obstructive CAD (Table 2). Age, hypertension, dyslipidaemia, CAC score, EATLM, and EATTotal are all associated with obstructive CAD. Patient characteristics of those with and without obstructive coronary disease are presented in Table 3. Using a stepwise multivariate logistic regression model, EATLM and EATTotal are found to be independently associated with obstructive CAD [OR: 1.204 per cm³ (95% CI: 1.028–1.411), \( P = 0.021 \) and OR: 1.007 per 10 cm³, (95% CI: 1.000–1.013), \( P = 0.038 \), respectively] (Table 2). When the CAC score [OR: 1.006, (95% CI: 1.004–1.009), \( P = 0.001 \)] was added to the multivariate logistic regression model, the association is lost for both EATLM and EATTotal [OR: 1.136 per cm³ (95% CI: 0.948–1.362), \( P = 0.168 \) and OR: 1.004 per 10 cm³, (95% CI: 0.996–1.011), \( P = 0.328 \), respectively] (Table 4).

Incremental predictive value of EAT for detecting obstructive CAD

ROC curve analysis failed to show any incremental value of adding BMI [AUC = 0.582 (95% CI: 0.49–0.67), \( P = 0.299 \)] to the NCEP risk score [AUC = 0.607 (95% CI: 0.53–0.68)] for detecting obstructive CAD. However, the addition of EATTotal [AUC = 0.709 (95% CI: 0.62–0.80), \( P = 0.009 \)] and that of EATLM [AUC = 0.717 (95% CI: 0.63–0.80), \( P = 0.003 \)] are both incremental to the NCEP score (Figure 4). When the CAC score was added to both the EATTotal model [AUC = 0.839, 95% CI: 0.78–0.90, \( P < 0.001 \)] and the EATLM model [AUC = 0.843, 95% CI: 0.79–0.90, \( P < 0.001 \)], there is a further significant gain in power to detect obstructive CAD (Figure 5).

Intra-observer and inter-observer reproducibility of EATLM

The intra-observer and inter-observer reproducibility calculated from a subset of 25 patients are excellent with ICC values of 0.997 (95% CI: 0.993–0.999) and 0.994 (95% CI: 0.986–0.998), respectively.

Discussion

The results of our study suggest that: (i) EATLM is highly correlated with EATTotal, (ii) EATLM and EATTotal are incremental to routine clinical predictors for obstructive CAD and (iii) the CAC score is a better predictor for the presence of CAD than EATLM or EATTotal. Though our analysis shows a statistically significant association between age, hypertension and dyslipidaemia, and obstructive CAD, no association is observed for smoking history, family history, BMI, diabetes, and male gender. The lack of statistical significance is likely due to the small population size.

The role of EAT in atherosclerosis

The biological effects of EAT and its association with CAD are complex. Studies show that EAT is capable of secreting pro-inflammatory substances such as TNF-α, IL-6, and monocyte chemotactant protein-1 (MCP-1); which may contribute to a pro-atherogenic milieu surrounding the coronary arteries supporting the observations that EAT burden is associated with CAD. Therefore, EAT may be a potentially useful clinical tool for the assessment of cardiac risk. Our study suggests that measuring EATLM is easy while maintaining a positive association with CAD.
Our study demonstrates that EATLM is highly correlated with EATTotal ($r = 0.89$, $P < 0.001$), which is consistent with Oyama et al. who also show that EATLM is highly correlated with EATTotal ($r = 0.92$). EATLM was chosen as the ideal surrogate since it is easily landmarked on CT scan and thus, likely has better reproducibility than slice measurements at other levels of the pericardium. As previously mentioned, the intra-observer and inter-observer reproducibility is excellent with ICC values of 0.997 and 0.994, respectively.

Prior studies support the association of EAT with CAD, which is echoed in the results of our study. Furthermore, the distribution of EAT, its proximity to coronary arteries, and local paracrine effects may be an important determinant of CAD. This would be consistent with proposed paracrine effects of adipose tissue to promote atherosclerotic progress. Other studies have indicated that the site of the EAT may be a factor in the development of coronary disease. Other studies have indicated that the site of the EAT may be a factor in the development of coronary disease.

Not surprisingly when the CAC score is incorporated into our predictive model there is a significant increase in power, which has been well documented in the literature. When CAC is incorporated into our multivariate logistic regression, both EATLM and EATTotal lose statistical significance. This is again not surprising, since the CAC score has an excellent ability to predict the presence of CAD (sensitivity 95% and specificity 66%).

EAT and risk stratification

Much of the focus to date has been on the association of EAT with existing CAD. Far fewer studies have examined the link between EAT and cardiovascular outcomes. Mahabadi et al. are able to

### Table 3  Baseline characteristics of patients with and without obstructive coronary artery disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Non-obstructive CAD (n = 145)</th>
<th>Obstructive CAD (n = 47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$53 \pm 11 \text{(27–87)}$</td>
<td>$60 \pm 8 \text{(38–81)}$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>BMI</td>
<td>$30.5 \pm 7.2 \text{(19.5–62.9)}$</td>
<td>$30.7 \pm 5.4 \text{(18.9–43.3)}$</td>
<td>$0.846$</td>
</tr>
<tr>
<td>Smoking</td>
<td>$75 \pm 5.17$</td>
<td>$29 \pm 6.17$</td>
<td>$0.131$</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$62 \pm 42.8$</td>
<td>$33 \pm 70.2$</td>
<td>$0.001$</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>$68 \pm 46.9$</td>
<td>$33 \pm 70.2$</td>
<td>$0.005$</td>
</tr>
<tr>
<td>Family history$^b$</td>
<td>$72 \pm 49.7$</td>
<td>$26 \pm 55.3$</td>
<td>$0.397$</td>
</tr>
<tr>
<td>Diabetes (type II and type 1)</td>
<td>$21 \pm 14.5$</td>
<td>$9 \pm 19.1$</td>
<td>$0.444$</td>
</tr>
<tr>
<td>Male gender</td>
<td>$75 \pm 51.7$</td>
<td>$26 \pm 55.3$</td>
<td>$0.668$</td>
</tr>
<tr>
<td>Agatston score</td>
<td>$46.4 \pm 125.3 \text{(0.0–995.0)}$</td>
<td>$443.7 \pm 447.50 \text{(0.0–1906.0)}$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>EATTotal (cm$^3$)</td>
<td>$118.1 \pm 54.2 \text{(39.1–434.0)}$</td>
<td>$151.0 \pm 55.9 \text{(46.4–246.0)}$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>EATLM (cm$^3$)</td>
<td>$3.5 \pm 2.1 \text{(0.6–14.9)}$</td>
<td>$4.8 \pm 2.2 \text{(1.6–9.4)}$</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Means ± SD (min –max) or number of patient (% of subset).

$^a$From a subset of 191 patients.

$^b$From a subset of 187 patients. Subset data are presented here due to unavailable data for a small number of patients in the registry.

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**EAT$_{LM}$ as an indirect measure of EAT$_{Total}$ and their relationship with CAD**

Our study demonstrates that EAT$_{LM}$ is highly correlated with EAT$_{Total}$ ($r = 0.89$, $P < 0.001$), which is consistent with Oyama et al. who also show that EAT$_{LM}$ is highly correlated with EAT$_{Total}$ ($r = 0.92$). EAT$_{LM}$ was chosen as the ideal surrogate since it is easily landmarked on CT scan and thus, likely has better reproducibility than slice measurements at other levels of the pericardium. As previously mentioned, the intra-observer and inter-observer reproducibility is excellent with ICC values of 0.997 and 0.994, respectively. Fortunately, Oyama et al. have already demonstrated EAT$_{LM}$ to be the best correlated with EAT$_{Total}$ when compared with measurements done at other levels.

Prior studies support the association of EAT with CAD, which is echoed in the results of our study. Furthermore, the distribution of EAT, its proximity to coronary arteries, and local paracrine effects may be an important determinant of CAD. This would be consistent with proposed paracrine effects of adipose tissue to promote atherosclerotic progress. Other studies have indicated that the site of the EAT may be a factor in the development of coronary disease, but our present study is the first to identify an association with EAT$_{LM}$ and obstructive coronary disease.

Not surprisingly when the CAC score is incorporated into our predictive model there is a significant increase in power, which has been well documented in the literature. When CAC is incorporated into our multivariate logistic regression, both EAT$_{LM}$ and EAT$_{Total}$ lose statistical significance. This is again not surprising, since the CAC score has an excellent ability to predict the presence of CAD (sensitivity 95% and specificity 66%).
### Table 4  Univariate and multivariate analysis of clinical characteristics including CAC for the presence of obstructive CAD

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis with EAT$_{Total}$</th>
<th>Multivariate analysis with EAT$_{LM}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.063</td>
<td>1.027–1.101</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.716</td>
<td>0.848–3.470</td>
<td>0.133</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.156</td>
<td>1.56–6.40</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2.67</td>
<td>1.319–5.402</td>
<td>0.006</td>
</tr>
<tr>
<td>Family history</td>
<td>1.332</td>
<td>0.686–2.585</td>
<td>0.398</td>
</tr>
<tr>
<td>BMI</td>
<td>1.005</td>
<td>0.958–1.054</td>
<td>0.845</td>
</tr>
<tr>
<td>Diabetes (type II and type 1)</td>
<td>1.398</td>
<td>0.591–3.309</td>
<td>0.445</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.156</td>
<td>0.597–2.238</td>
<td>0.668</td>
</tr>
<tr>
<td>EAT$_{Total}$ (per 10 cm$^3$)</td>
<td>1.104</td>
<td>1.041–1.172</td>
<td>0.001</td>
</tr>
<tr>
<td>EAT$_{LM}$ (per 1 cm$^3$)</td>
<td>1.303</td>
<td>1.119–1.516</td>
<td>0.001</td>
</tr>
<tr>
<td>CAC</td>
<td>1.007</td>
<td>1.005–1.010</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Figure 4** Incremental power of epicardial adipose tissue in the assessment of obstructive CAD. BMI (AUC = 0.582, 95% CI: 0.49–0.67, \( P = 0.299 \)) provided no incremental value to NCEP (AUC = 0.607, 95% CI: 0.53–0.68) in predicting obstructive CAD. The addition of EAT$_{Total}$ (AUC = 0.709, 95% CI: 0.62–0.80, \( P = 0.009 \)) and EAT$_{LM}$ (AUC = 0.717, 95% CI: 0.63–0.80, \( P = 0.003 \)) to the model both showed statistically significant increases in power.
demonstrate in a sample of 1267 patients that epicardial fat is associated with prevalent coronary heart disease including myocardial infarction and angina though the association is lost when traditional risk factors are included. Later, Cheng et al.\(^\text{23}\) performed a small case–control study, which shows that epicardial fat is associated with cardiac death, myocardial infarction, stroke, and late revascularization at 4 years. This association is preserved even after adjustment for Framingham Risk Score and CAC score.

Both EAT\textsubscript{LM} and EAT\textsubscript{Total} have incremental value over traditional risk factors in predicting obstructive CAD. Whether EAT\textsubscript{LM} or EAT\textsubscript{Total} correlates with atherosclerosis prior to its calcification or predicts coronary events requires further investigation. The results of this study suggest that this measure may be useful in patients where CAC is not calculated.

### Echocardiography and magnetic resonance imaging

Some attempts to quantify EAT with echocardiography in the past have shown very good intra- and inter-observer agreement (ICC 0.94–0.98 and 0.94–0.96, respectively).\(^\text{24,25}\) However, limitations inherent to the technique may make it less than optimal as a tool to measure EAT. Specifically, measurements have been limited to segments of EAT in the right ventricular free wall. Furthermore, a comparison of echocardiography EAT measurements with CT shows very poor correlation.\(^\text{26}\) Conversely, MRI would provide equally excellent measures of EAT but may be limited by availability.

### Limitations

This is a single-centre study with 192 patients. Confirmation of the study findings should be performed in larger populations. Since our study population is comprised of those having symptoms, our ability to generalize the results to asymptomatic individuals requires further study. The outcome measure in the present study is obstructive coronary disease. Hard clinical outcomes are not assessed but this should be the aim of future investigations into the role of EAT\textsubscript{LM} to predict the clinical course of CAD.

### Conclusion

EAT\textsubscript{LM} appears to be an efficient and clinically practical measure of EAT\textsubscript{Total}, and both appear to be independent and incremental predictors of obstructive CAD.
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