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## Epicardial and Paracardial Adipose Tissue Volume and Attenuation – Association with High-Risk Coronary Plaque on Computed Tomographic Angiography in the ROMICAT II Trial

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### Abstract

**Background and aims**—To determine whether epicardial (EAT) and paracardial adipose tissue (PAT) volume and attenuation are associated with high-risk coronary plaque features.

**Methods**—In subjects with suspected acute coronary syndrome (ACS) enrolled in the ROMICAT II trial, EAT and PAT volumes indexed to body surface area (BSA) and attenuation were measured on noncontrast coronary artery calcium score (CACS) CT. High-risk plaque features (napkin-ring sign, positive remodeling, low density plaque, spotty calcium) and stenosis were assessed on coronary CT angiography (CTA). The association of EAT and PAT volume and attenuation with

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#### Author contributions

MTL and JP contributed equally to the manuscript.

high-risk plaque and whether this was independent of clinical risk assessment, CACS and significant coronary artery disease (CAD) was determined.

**Results**—Of 467 (mean 54±8 yrs, 53% male) with CACS and CTA, 167 (36%) had high-risk plaque features. Those with high-risk plaque had significantly higher indexed EAT (median 59 (Q1–Q3:45–75) cc/m<sup>2</sup> vs. 49 (35–65) cc/m<sup>2</sup>,  $p < 0.001$ ) and PAT volume (median:51 (36–73) cc/m<sup>2</sup> vs. 33 (22–52) cc/m<sup>2</sup>,  $p < 0.001$ ). Higher indexed EAT volume was associated with high-risk plaque [univariate OR 1.02 (95%-CI:1.01 – 1.03) per cc/m<sup>2</sup> of EAT,  $p < 0.001$ ], which remained significant [univariate OR 1.04 (95%-CI:1.00–1.08) per cc/m<sup>2</sup> of EAT,  $p = 0.040$ ] after adjustment for risk factors, CACS, and stenosis > 50%. Higher indexed PAT volume was associated with high-risk plaque in univariate analysis [OR 1.02 (1.01 – 1.03) per cc/m<sup>2</sup> of PAT,  $p < 0.001$ ], though this was not significant in multivariate analysis. At a threshold of >62.3 cc/m<sup>2</sup>, EAT volume was associated with high-risk plaque [univariate OR 2.50 (95%-CI:1.69–3.72),  $p < 0.001$ ], which remained significant [OR 1.83 (95%-CI:1.10–3.05),  $p = 0.020$ ] after adjustment. Subjects with high-risk plaque had lower mean attenuation EAT (–88.1 vs. –86.9 HU,  $p = 0.008$ ) and PAT (–106 vs. –103 HU,  $p < 0.001$ ), though this was not significant in multivariable analysis.

**Conclusions**—Greater volumes of EAT are associated with high-risk plaque independent of risk factors, CACS and obstructive CAD. This observation supports possible local influence of EAT on development of high-risk coronary plaque.

### Keywords

Coronary CT Angiography; high-risk coronary plaque; coronary atherosclerosis; epicardial adipose tissue; paracardial adipose tissue

### Introduction

Epicardial adipose tissue (EAT), defined as fat within the pericardial sac, is a metabolically and immunologically active fat depot implicated in atherogenesis. EAT encases the coronary arteries without an intervening fascial barrier<sup>1</sup>. EAT also shares common innervation and blood supply with the coronary arterial wall. Due to this unique anatomic relationship, several authors have suggested that inflamed EAT may release cytokines with a local paracrine proatherogenic effect on the underlying coronary arteries<sup>2, 3</sup>. By this mechanism EAT may be the link between dysregulated metabolism, inflammation of the arterial wall and subsequent atherogenesis. Paracardial adipose tissue (PAT) lies outside the external surface of the pericardium, with separate blood supply from the pericardiophrenic artery<sup>4</sup>. PAT may also potentiate atherogenesis through endocrine mediators, though this has not yet been clarified.

Cardiac computed tomography allows for both accurate quantification of EAT/PAT<sup>5–7</sup> and identification of high-risk coronary plaque features. High-risk plaque features include positive remodeling, low-density plaque <30 Hounsfield Units (HU), spotty calcification, and napkin ring sign and are associated with future adverse cardiovascular events<sup>8–13</sup>. The volume of EAT has been linked to coronary risk factors, coronary artery calcification, plaques causing significant (>50%) stenosis, and adverse events<sup>6, 14–19</sup>. Furthermore, the “quality” of fat can also be evaluated via CT attenuation (density) measurements. While

lower CT density of visceral and subcutaneous abdominal fat have been linked to greater extent of coronary artery calcium<sup>20</sup> and cardiovascular events<sup>21</sup> in the Framingham Heart Study, the relationship between epicardial and paracardial fat attenuation and high-risk plaque features is not well understood.

Similarly, the evidence linking the quantity of epicardial and paracardial fat depots with high-risk coronary plaque features is limited. The aim of this study was to investigate the association between the quantity and density of EAT and PAT and high-risk coronary plaque seen on coronary CT angiography (CTA). Furthermore, we examined whether this association is independent of traditional cardiovascular risk factors, coronary artery calcification, and coronary artery stenosis.

## Patients and methods

### Study population

The study cohort consisted of subjects randomized to CTA in the ROMICAT II trial. The trial was designed to compare CTA versus standard evaluation for suspected acute coronary syndrome (ACS) in the emergency department. A detailed description of the patient population and CT protocol was recently reported<sup>22</sup>. Briefly, 1,000 patients presenting to the emergency department of nine hospitals in the United States with chest pain, clinical suspicion of acute coronary syndrome, and no known history of CAD were enrolled between April 2010 and January 2012. Of these, 501 were randomized to CT and had both prospectively ECG-triggered non-contrast coronary artery calcium scoring (CACS) CT to evaluate for coronary artery calcium and contrast-enhanced retrospectively ECG-gated or prospectively ECG-triggered CTA to evaluate for coronary artery stenosis (Supplemental Figure 1). CT images were acquired using a 64 multi-detector row or more recent scanner<sup>23</sup>. Baseline clinical characteristics, medical history and cardiovascular risk factors (arterial hypertension, hyperlipidemia, diabetes mellitus, and former or current smoking) were collected<sup>22</sup>. Body mass index (BMI) was calculated as body weight divided by the square of height. Body surface area (BSA) was calculated using the Mosteller formula.

Previous investigations of the trial's CTA cohort found that those with high-risk coronary plaque on CT were more likely to have ACS<sup>13</sup>, and that non-alcoholic fatty liver disease is associated with high-risk plaque<sup>24</sup>. There have been no previous investigations of epicardial or paracardial fat in this cohort. All study participants provided written consent, and local institutional review boards approved the study.

### Noncontrast CT assessment of epicardial and paracardial adipose tissue

Epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT) were measured on the non-contrast CACS images. For the purposes of this study, epicardial adipose tissue (EAT) was defined as fat within the pericardial sac. Paracardial adipose tissue (PAT) was defined as fat along the external surface of the pericardium<sup>1</sup>. We defined total adipose tissue (TAT) as the sum of EAT and PAT. It is worth acknowledging another commonly used term for fat around the heart – pericardial adipose tissue. Some authors use pericardial adipose tissue

synonymously with EAT<sup>25</sup>; others define pericardial adipose tissue as the sum of EAT and PAT<sup>4</sup>. In light of this inconsistency, we elected to use the above definitions of EAT and PAT.

Measurement of EAT and PAT volume and mean attenuation was performed using the non-contrast CACS CTs on a dedicated offline workstation (Volume Viewer, Siemens Medical Solutions, Forchheim, Germany) using a semi-automated technique divided between a team of two readers (at least 1 year of experience in cardiac CT) blinded to the results of the CTA. For EAT, regions of interest (ROI) were manually drawn tracing the contour of the pericardium at 1 cm intervals, starting at the mid-level of the right pulmonary artery and extending inferiorly to the diaphragm. Interpolated contours were manually adjusted as necessary<sup>16</sup>. For PAT, ROIs were drawn around the adipose tissue outside the pericardial sac. As suggested in previous literature, attenuation thresholds of -195 to -45 HU were applied to identify voxels containing adipose tissue<sup>14</sup>. Volume and mean attenuation of adipose tissue was recorded in cubic centimeters (cc) and Hounsfield units (HU), respectively. Twenty-five randomly chosen subjects' EAT and PAT measurements were analyzed by both readers to assess inter-observer variability. (Figure 1)

### **CTA assessment of high-risk coronary plaque (primary outcome)**

The contrast-enhanced CTA images were divided between a second team of three core laboratory CTA readers (at least 5 years of experience in cardiac CTA and level III training), who performed the image analysis of coronary plaque and high-risk plaque features on a dedicated cardiac workstation (TeraRecon, San Mateo, CA). The CTA analysis was performed on a per coronary segment basis using the model of the Society of Cardiovascular Computed Tomography<sup>26</sup>. For each coronary segment, the reader determined whether the image quality was sufficient to evaluate for the presence of stenosis and plaque with confidence. Coronary segments that were assessed as non-diagnostic in image quality were treated as non-informative for the purpose of the analysis.

The CTA readers assessed each evaluable coronary segment for noncalcified plaque, calcified plaque, and stenosis  $\geq 50\%$  as previously described<sup>8</sup>. The primary outcome was the presence of one or more high-risk plaque features which were defined as positive remodeling, low Hounsfield unit (HU) plaque, napkin-ring sign and spotty calcium (Supplemental Figure 2). Positive remodeling was analyzed on long and short axis multiplanar reformatted images, and defined by a ratio of at least 1.1 of the maximal outer diameter of the vessel at the plaque divided by the average of the diameter of proximal and distal normal reference vessels<sup>27</sup>. If a low density non-calcified plaque was noted, readers placed three region-of-interest measurements (approximately 0.5 – 1.0 mm<sup>2</sup>) in the non-calcified low density, with low HU plaque defined as a mean HU number  $<30$  HU<sup>28</sup>. The napkin-ring sign was defined as ring of peripheral higher attenuation surrounding a central core of low attenuation in a non-calcified coronary plaque<sup>29, 30</sup>. Spotty calcium was defined by calcified plaque with measuring  $<3$  mm, extending  $<1.5$  times the vessel diameter along the long axis of the vessel, and occupying two thirds of the circumference of the vessel<sup>31</sup>.

## Statistical analysis

All statistical analyses were performed using Stata 13.1 (StataCorp LP, College Station, Texas). Continuous data are presented as mean  $\pm$  standard deviation or median with interquartile ranges. Categorical and ordinal variables are presented as absolute and relative frequencies. Comparisons between groups were performed with the use of an unpaired Student's t-test or Wilcoxon rank-sum test for continuous variables, Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables. Inter-observer variability for volume and mean attenuation was assessed using the intra-class correlation coefficient (ICC).

To determine the association between high-risk plaque features and (continuous) EAT volume, we performed univariable (i.e. unadjusted) and multivariable (i.e. adjusted) logistic regression analyses. The models included the presence of high-risk plaque as dependent variable, absolute and BSA-indexed fat depot volume, fat depot attenuation, age, sex, number of cardiovascular risk factors, (log) calcium score, and obstructive CAD ( $\geq 50\%$  stenosis) as independent variables. To address any possible non-linear relationship, i.e. convex or concave, we also added a quadratic variable (Squared Indexed Epicardial Fat Volume/Squared Indexed Paracardial Fat Volume) to each regression model.

In order to provide a potentially clinically useful threshold for "high" EAT volume, an optimal cutoff value for EAT regarding high-risk plaque features was then calculated using the maximum sum of sensitivity and specificity in ROC analysis. The association between high-risk plaque features and the (binary) EAT measurement based on the cutoff value was then performed in univariate and stepwise multivariate logistic regression analyses, excluding variables with  $p > 0.10$ . The above analyses were then repeated for PAT. For all analyses, a 2-tailed  $p$  value  $< 0.05$  was required to reject the null hypothesis.

## Results

### Study population and high-risk plaque features

Of the 501 subjects randomized to the CTA arm of the ROMICAT II trial, 28 were excluded who did not undergo CT, 1 due to insufficient image quality of the CTA, and 5 who did not undergo non-contrast CT (Supplemental Figure 1). 467 subjects (mean age  $54 \pm 8$  yrs, 47 % female) who underwent both contrast CTA and non-contrast CACS imaging with diagnostic quality were included in the analysis. Baseline characteristics are described in Table 1.

On CTA, 36% (167/467) had high-risk plaque features which were more prevalent in male ( $p < 0.001$ ), older ( $p < 0.001$ ) and obese ( $p = 0.046$ ) subjects. The frequencies of the individual high-risk plaque features among the subjects with high-risk plaque were as following: Napkin-ring sign 15.0%, positive remodeling 32.3%, low HU plaque 23.4% and spotty calcium 91.0%. The overall number of risk factors was greater among subjects with high-risk plaque features ( $p < 0.001$ ), with a higher rate of hypertension ( $p = 0.003$ ), diabetes ( $p = 0.039$ ), dyslipidemia ( $p < 0.001$ ) and smoking ( $p = 0.005$ ).

CAD was present in 260 (56%), with non-obstructive CAD ( $< 50\%$  stenosis) in 216 (46%) and obstructive CAD ( $\geq 50\%$  stenosis) in 44 (9%) subjects (Table 2). Coronary artery

calcium was present in 217 (46%) subjects. Stenosis and calcium were more prevalent in subjects with high-risk plaque ( $p < 0.001$ ).

### Inter-rater agreement

EAT and PAT measurements were highly reproducible between the two EAT/PAT readers, with excellent inter-rater agreement for EAT volume (ICC = 0.994), PAT volume (ICC = 0.991), EAT mean attenuation (ICC = 0.849) and PAT mean attenuation (ICC = 0.988) (Supplemental Figure 3).

### Fat volume and density

Subjects with high-risk plaque showed a higher median EAT volume than those without high-risk plaque [123 (IQR 93 – 156) cc vs. 98 (IQR 68–127) cc,  $p < 0.001$ ]. PAT volume was significantly higher in subjects with high-risk plaque than in those without [107 (IQR 69 – 157) cc vs. 68 (IQR 42 – 103) cc,  $p < 0.001$ ] (Table 2).

Figure 4-2 illustrates EAT volume stratified by BMI categories and the presence of high-risk plaque features. Subjects with high-risk plaque had significantly higher EAT volume for all four standard BMI categories including subjects with a BMI  $< 25$  (all with  $p = 0.05$ ). Similar significant differences across BMI categories were observed for PAT (Supplemental Figure 4). We then indexed EAT and PAT volumes to body surface area to adjust for metabolic mass independent of body habitus. Indexed EAT and PAT volumes remained significantly higher in subjects with high-risk plaque (both  $p < 0.001$ ).

In subjects with high-risk plaque, the median EAT density was lower by one Hounsfield unit compared to subjects without high-risk plaque [–88 HU vs. –87 HU,  $p = 0.008$ ]. For PAT, the median density was lower by 3 HU [–106 vs. –103 HU,  $p < 0.001$ ] for subjects with high-risk plaque (Table 2).

### Association of EAT and PAT volume with high-risk plaque – Continuous approach

With EAT treated as a continuous variable, higher indexed EAT volume was associated with high-risk plaque [univariate OR 1.02 (95%-CI:1.01 – 1.03) per  $\text{cc}/\text{m}^2$  of EAT,  $p < 0.001$ ], which remained significant (multivariate OR 1.04 (95%-CI:1.00–1.08) per  $\text{cc}/\text{m}^2$  of EAT,  $p = 0.040$ ) after adjustment for the number of risk factors, CACS, and stenosis  $\geq 50\%$  (Table 3). Higher indexed PAT volume was associated with high-risk plaque in univariate analysis [OR 1.02 (1.01 – 1.03) per  $\text{cc}/\text{m}^2$  of PAT,  $p < 0.001$ ], though this was not significant in multivariate regression analysis [OR 1.01 (0.99 – 1.044),  $p = 0.22$ ].

### Association of EAT and PAT volume with high-risk plaque – Threshold approach

The optimal threshold which maximized the sensitivity and specificity of indexed EAT volume for prediction of high-risk plaque was  $62.3 \text{ cc}/\text{m}^2$ , with a sensitivity of 48.5% (95% CI 40.7–56.3%) and a specificity of 72.7% (95% CI 67.2–77.6%). For indexed PAT the optimal cut-point was  $33.6 \text{ cc}/\text{m}^2$ . An indexed EAT volume greater than  $62.3 \text{ cc}/\text{m}^2$  was significantly associated with high-risk plaque [univariate odds ratio (OR): 2.50 (CI 1.69 – 3.72),  $p < 0.001$ ]. In the stepwise logistic regression analysis, the association remained significant [OR 1.83 (CI 1.11 – 3.05),  $p = 0.020$ ] after adjustment for female sex [OR 0.42



(CI 0.25 – 0.70),  $p=0.001$ ], CACS [OR 1.75 (1.56 – 1.97),  $p<0.001$ ], and stenosis 50% [OR 5.19 (CI 1.64 – 16.41),  $p=0.005$ ]. Age and the number of cardiovascular risk factors were excluded from the model since they did not meet the criteria of  $p<0.1$  (Table 4).

Similarly, indexed PAT volumes greater than 33.6 cc/m<sup>2</sup> were significantly associated with high-risk plaque in uni- and multivariable analysis. For indexed PAT, the number of cardiovascular risk factors was excluded from the model as it did not meet the prespecified criteria of  $p<0.1$  (Table 4).

The cut-offs and odds ratios for absolute (non-indexed) EAT and PAT volumes can be found in Supplemental Table 2b. Both absolute EAT and PAT volumes were significant predictors of high-risk plaque in univariable analysis. However in multivariable analysis only absolute EAT volume remained a significant predictor of high-risk plaque [adjusted OR 1.88 (CI 1.14 – 3.10),  $p=0.013$ ].

Cutoffs and odds ratios for absolute and BSA-indexed total adipose tissue (EAT + PAT) are described in Supplemental Table 1b. Both absolute and indexed total adipose tissue volume had a significant association with high-risk plaque; however in multivariable analysis only the indexed total fat volume was significant [adjusted OR 1.74 (CI 1.05 – 2.88),  $p=0.031$ ].

## Discussion

In 467 subjects with acute chest pain who had both non-contrast CT and CTA, we found a significant association between excess epicardial adipose tissue volume and high-risk plaque features, which persisted after adjusting for potential confounders such as traditional cardiovascular risk factors, coronary artery calcium score, and coronary artery stenosis. In addition, lower attenuation EAT and PAT were associated with high-risk plaque features, but only in univariate analyses. These findings support the possible local influence of epicardial adipose tissue depots on high-risk coronary plaque features.

### EAT volume and high-risk plaque

In multivariate analyses we found that each additional cc/m<sup>2</sup> of EAT was associated with an 1.04 fold higher odds of having high risk coronary plaque (OR 1.04 (1.00–1.08),  $p=0.040$ ). These results add to the body of evidence linking EAT and coronary atherosclerosis. There is no fascial barrier between EAT and the coronary arteries it encases. Due to this unique anatomic relationship, EAT and the coronaries share a common blood supply and innervation<sup>32</sup>. In animal models selective surgical excision of EAT slows atherosclerosis in the underlying coronary artery<sup>33</sup>. Analysis of excised human specimens<sup>2</sup> suggests that EAT secretes cytokines with a paracrine proatherogenic effect on the underlying coronary arteries<sup>14, 15, 34</sup>. Furthermore on a local level, increased EAT around a coronary artery segment detected on CT is associated with increased CAD in that segment, including high-risk plaque features<sup>35–40</sup>.

Several studies have demonstrated an association between EAT volume and risk factors, progression of coronary artery calcification, plaques causing significant (>50%) stenosis, and adverse events<sup>6, 14–19, 41</sup>. Two studies have found an association between the volume of

EAT and high-risk plaque features<sup>16, 42</sup>. Our findings extend these studies by assessing for independence from coronary calcium score and significant stenosis to adjust for established predictors of cardiovascular risk<sup>43</sup> in the setting of a multicenter randomized controlled trial. We also provide results indexed to body surface area to adjust for changes related to habitus that are known to alter EAT volume<sup>44</sup>. These findings suggest that EAT is associated with specific features representing high-risk plaque independent of general features of CAD such as CAC or degree of stenosis, and support the hypothesis that fat depot inflammation plays a role in the development of high-risk coronary plaque. While information about EAT is of limited additional value when patients already undergo evaluation with contrast ECG-gated coronary CTA, which allows direct visualization of high risk plaque features, excess EAT may be useful to identify persons at high risk who have only non-contrast CT or a non-ECG gated CTA.

### **EAT, PAT and VAT**

Epicardial and visceral adipose tissue (VAT) share the same embryological origin and show similar morphological and physiological characteristics<sup>4</sup>. Although VAT is not measurable on standard cardiac CT, we accounted for other anthropometric variables using body surface area and BMI. Our findings are supported by sub-analyses of the Framingham Heart and the Jackson Heart Study, in which EAT was associated with coronary calcification and an adverse cardiovascular risk profile after correction for VAT, respectively<sup>6, 14, 45</sup>. Doesch et al. report that indexed and absolute EAT volumes quantified by cardiac magnetic resonance imaging were lower in subjects with a clinical diagnosis of ischemic heart failure (NYHA II) compared to a healthy control group. These findings suggest a possible dynamic character of EAT volume that evolves with the severity of ischemic cardiomyopathy<sup>46</sup>. However as the ROMICAT II population consisted of persons at low to intermediate risk for CAD and no known history of CAD, we expect that most were in the early phase of disease. EAT was more strongly associated with high risk plaque than PAT. A significant association between EAT and high risk plaque was found in all analyses, whereas PAT fell out of the analysis when assessed as a continuous variable or when not indexed to BSA. These observations are concordant with those of Chen et al. which found excess PAT volume to be associated with the presence of metabolic syndrome but not with CAD<sup>47</sup>. High amounts of PAT were shown to be closely connected to VAT, metabolic risk factors and further hypothesized to be a surrogate for overall obesity<sup>48</sup>. EAT is the true visceral fat of the heart and shares the vascular supply as the coronary arteries without an intervening fascial barrier, and thus could have a local paracrine effect on the coronary arteries. In contrast PAT lies outside the pericardial sac, and thus may have a less direct effect.

### **Volume thresholds in comparison to published values**

We analyzed first EAT and PAT as continuous variables, then as binary variables using a threshold approach. Thresholds can be useful to define a “high” volume in clinical practice. Our volume thresholds for EAT were similar to those previously reported to be “high” or associated with adverse events. Our BSA-indexed EAT threshold of 62.3 cc/m<sup>2</sup> was slightly below the 68 cc/m<sup>2</sup> reported to be at the 95<sup>th</sup> percentile in a healthy population<sup>49</sup>. We calculated an absolute EAT threshold of 117 cc for optimal prediction of high-risk plaque



features (Supplemental Table 2a); this was also slightly below the cutoff of 125 cc described as a predictor of major adverse cardiac events in an asymptomatic population<sup>50</sup>.

### **CT attenuation of EAT/PAT and high-risk plaque**

Subjects with high-risk plaque had slightly lower mean attenuation of both EAT [−88 HU vs. −87 HU,  $p=0.008$ ] and PAT [−106 vs. −103 HU,  $p<0.001$ ]. While the magnitude of the attenuation difference was small (between one and three HU) and there was not an independent association in multivariate analysis, these hypothesis-generating data raise the possibility that the quality of epicardial and paracardial fat play a role in the development of high-risk plaque features. Furthermore the overall lower mean density of PAT relative to EAT suggests an underlying difference in the makeup of these adjacent but embryologically distinct fat depots. Our findings extend similar observations in the Framingham Heart Study in which lower visceral and subcutaneous fat mean attenuation was associated with an adverse cardiometabolic risk profile<sup>21</sup>, coronary calcification<sup>20</sup>, and death<sup>51</sup>. It is hypothesized that lower CT density of fat is the result of poor vascularization and lipid dense fat tissue<sup>20</sup>. Conversely, higher fat density might be a CT-morphological correlate for inflammation<sup>52</sup> or fibrosis<sup>53</sup>. The interplay between high-risk coronary plaque and adipose density and how these changes are reflected in CT morphology requires further investigations.

### **Strengths and limitations**

Strengths include a relatively large, well-defined subject cohort from a multi-center randomized clinical trial. A potential limitation lies in the cross-sectional nature of the study which only allows us to infer associations, not causality. Furthermore, our subject cohort consisted of patients 40–74 years old referred for acute chest pain, and thus may not be generalizable to the broader population without acute chest pain for whom high-risk plaque is presumably less common. PAT often extends above and below the heart, and thus the full extent of PAT may not have been captured due to limited z-axis coverage on these coronary calcium score CTs. Lastly, the pathophysiological mechanisms which connect the morphological characteristics of these fat depots to the formation of high-risk plaque features have yet to be fully uncovered.

### **Conclusion**

Greater volumes of EAT are associated with high-risk plaque in patients referred for acute chest pain independent of traditional risk factors, CACS and stenosis. These observations suggest that local ectopic adipose tissue may play a role in the development of high-risk coronary plaque.

### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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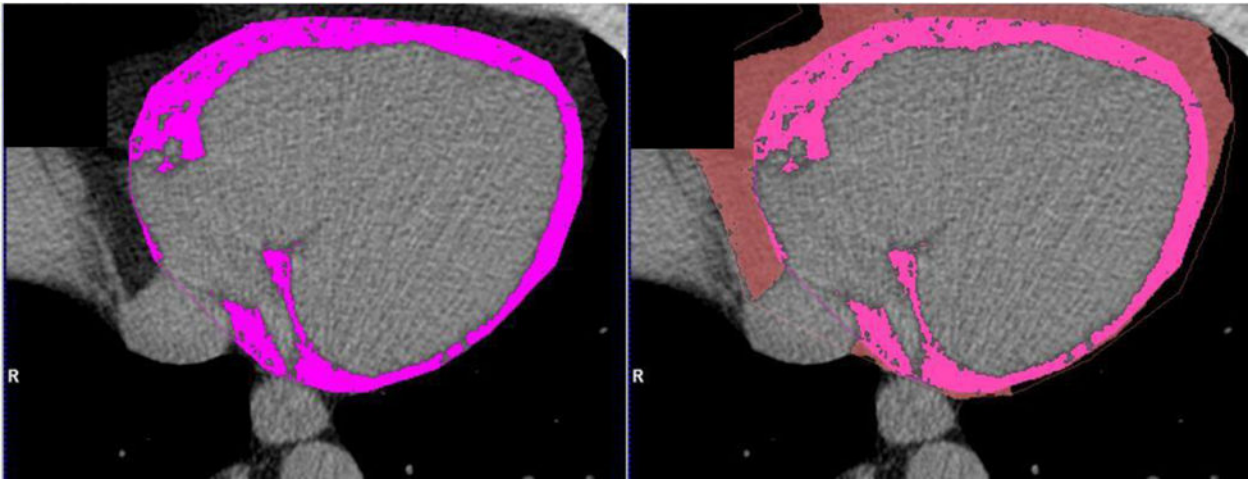
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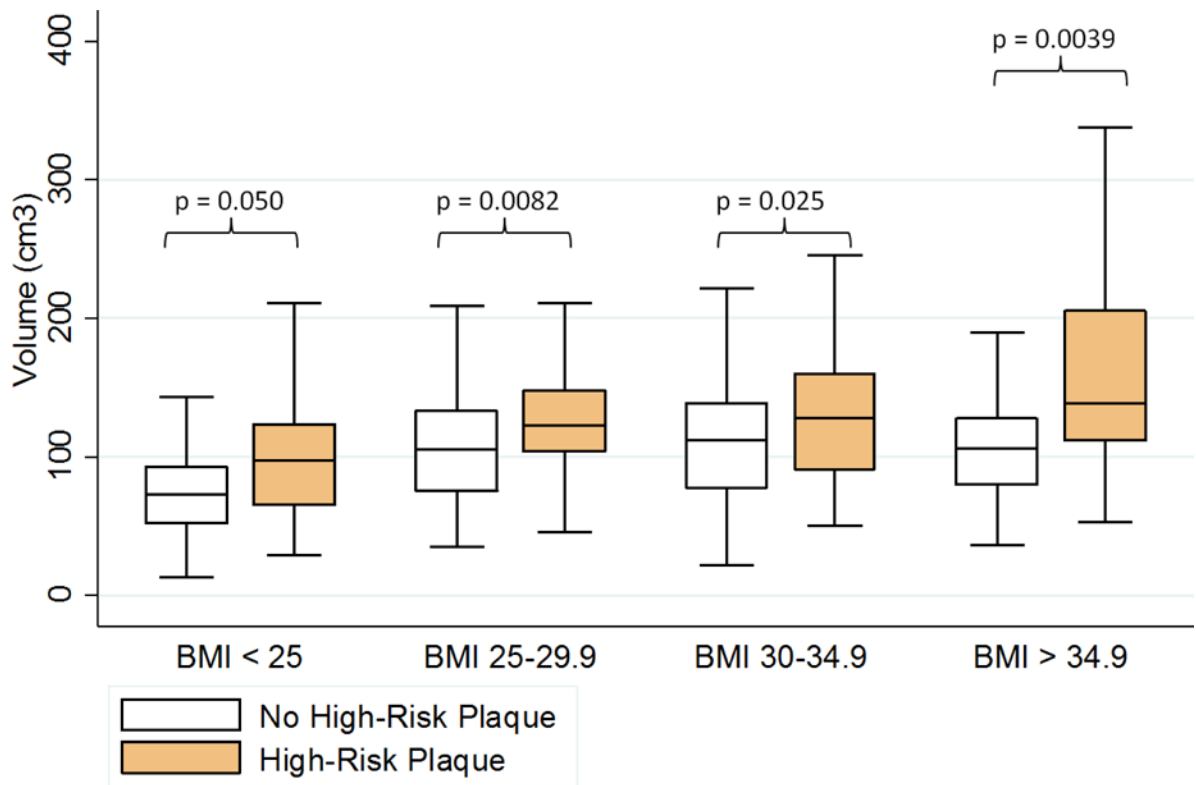
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**Figure 1. Non-Contrast CT measurements of epicardial and paracardial adipose tissue (EAT and PAT)**

Epicardial adipose tissue within the pericardium (left) and paracardial adipose tissue outside the pericardium (right) are traced manually. Voxels with attenuation between  $-195$  and  $-45$  HU (fat tissue) are marked in pink for EAT and salmon for PAT.





**Figure 2.**

Absolute epicardial adipose tissue volume is increased in individuals with high-risk coronary plaque features within across BMI categories.

**Table 1**

## Clinical Characteristics of Study Patients

	<b>Total (n = 467)</b>	<b>High-risk Plaque (n = 167)</b>	<b>No High-risk Plaque (n = 300)</b>	<b>p value</b>
Age (mean $\pm$ SD), years	53.9 $\pm$ 8.0	56.8 $\pm$ 8.4	52.3 $\pm$ 7.3	<0.001
Female sex, n (%)	221 (47.3)	49 (29.3)	172 (57.3)	<0.001
Body Mass Index (mean $\pm$ SD), kg/m <sup>2</sup>	29.4 $\pm$ 5.1	30.0 $\pm$ 4.7	29.1 $\pm$ 5.3	0.046
Cardiovascular risk factors, n (%)				
Hypertension	249 (53.3)	105 (62.9)	144 (48.0)	0.003
Diabetes mellitus	78 (16.7)	36 (21.6)	42 (14.0)	0.039
Dyslipidemia	212 (45.4)	98 (58.7)	114 (38.0)	<0.001
Former or current smoker	233 (49.9)	98 (58.7)	135 (45.0)	0.005
Family history of premature CAD	130 (27.8)	38 (22.8)	92 (30.7)	0.085
Number of cardiovascular risk factors, %				<0.001
0 or 1	170 (36.4)	43 (25.8)	128 (42.3)	
2 or 3	253 (54.2)	98 (58.7)	155 (51.7)	
4	44 (9.4)	26 (15.6)	18 (6.0)	

**Table 2**

Coronary Computed Tomography Angiography Characteristics of Patients Stratified According to Presence of Any High-risk Plaque

	Total (n = 467)	High-risk Plaque (n = 167)	No High-risk Plaque (n = 300)	<i>p</i> value
Coronary Artery Disease (CAD) category, n (%)				
No CAD (0% Stenosis)	207 (44.3)	0 (0)	207 (69.0)	—
Mild CAD (1–49% Stenosis)	216 (46.3)	127 (76.1)	89 (29.7)	<0.001
Significant CAD (≥ 50% Stenosis)	44 (9.4)	40 (24.0)	4 (1.3)	<0.001
Coronary Artery Calcium Score Category, n (%)				
CACS 0	250 (53.5)	14 (8.4)	236 (78.7)	<0.001
CACS 1 – 100	137 (29.3)	93 (55.7)	44 (14.7)	
CACS 101 – 300	42 (9.0)	30 (18.0)	12 (4.0)	
CACS > 300	38 (8.1)	30 (18.0)	8 (2.7)	
Epicardial Fat Measurements, median (iqr)				
Fat Volume [cc]	108.5 (76.4 – 140.6)	123.0 (93.4 – 155.8)	97.9 (68.2 – 126.5)	<0.001
Indexed Fat Volume [cc/m <sup>2</sup> ]	53.7 (37.8 – 69.4)	59.2 (45.2 – 75.2)	49.2 (35.2 – 64.9)	<0.001
Mean Attenuation [HU]	–87.3 (–90.2 – –85.0)	–88.1 (–90.9 – –85.7)	–86.9 (–89.9 – –84.7)	0.008
Paracardial Fat Measurements, median (iqr)				
Fat Volume [cc]	79.0 (46.2 – 128.3)	106.8 (68.9 – 157.1)	67.8 (42.1 – 103.1)	<0.001
Indexed Fat Volume [cc/m <sup>2</sup> ]	40.4 (24.4 – 60.6)	50.5 (36.1 – 73.3)	33.4 (22.1 – 52.2)	<0.001
Mean Attenuation [HU]	–104.8 (–108.9 – –100.5)	–106.4 (–110.6 – –102.7)	–103.4 (–107.5 – –99.6)	<0.001
Total Fat Measurements <sup>a</sup> , median (iqr)				
Fat Volume [cc]	189.3 (129.1 – 261.2)	232.8 (169.8 – 324.2)	166.8 (113.8 – 242.1)	<0.001
Indexed Fat Volume [cc/m <sup>2</sup> ]	96.6 (68.1 – 127.0)	113.4 (86.5 – 149.6)	84.9 (60.6 – 118.9)	<0.001
Mean Attenuation [HU]	–94.9 (–98.6 – –91.9)	–96.9 (–99.7 – –93.8)	–93.8 (–97.5 – –91.0)	<0.001

CAD = Coronary artery disease; CACS = Coronary artery calcium score;

<sup>a</sup>Total fat = epicardial + paracardial fat

**Table 3**

Unadjusted and Adjusted Associations Between Continuous Epicardial and Paracardial Fat Volume, Demographic/Clinical Risk Factors, and High-risk Plaque Features

Dependent Variable: Any High-risk Plaque Feature Independent Variables	Univariable Analysis		Multivariable Analysis Model: EAT (indexed volume)		Multivariable Analysis Model: PAT (indexed volume)	
	Unadjusted OR	p value	Adjusted OR	p value	Adjusted OR	p value
Indexed Epicardial Fat Volume (continuous, cc/m <sup>2</sup> )	1.02 (1.01–1.03)	<0.001	1.04 (1.00–1.08)	0.040	NA	NA
Squared Indexed Epicardial Fat Volume	1.00 (1.00–1.00)	0.001	1.00 (1.00–1.00)	0.031	NA	NA
Indexed Paracardial Fat Volume (continuous, cc/m <sup>2</sup> )	1.02 (1.01–1.03)	<0.001	NA	NA	1.01 (0.99–1.04)	0.215
Squared Indexed Paracardial Fat Volume	1.00 (1.00–1.00)	<0.001	NA	NA	1.00 (1.00–1.00)	0.065
Age (years)	1.08 (1.05–1.10)	<0.001	1.03 (1.00–1.07)	0.074	1.04 (1.00–1.08)	0.030
Female	0.31 (0.21–0.46)	<0.001	0.36 (0.21–0.63)	0.001	0.34 (0.19–0.63)	<0.001
No. of cardiovascular risk factors <sup>a</sup>	1.48 (1.24–1.76)	<0.001	1.05 (0.84–1.32)	0.655	1.09 (0.86–1.37)	0.478
Coronary artery calcium score (log)	1.91 (1.71–2.13)	<0.001	1.69 (1.49–1.93)	<0.001	1.71 (1.50–1.94)	<0.001
Significant CAD ( > 50% Stenosis)	23.31 (8.17–66.51)	<0.001	5.66 (1.73–18.51)	0.004	4.97 (1.53–16.20)	0.008

The summary is based on all 467 observations; 95% Confidence Intervals in brackets

<sup>a</sup>Risk factors include arterial hypertension, diabetes mellitus, dyslipidemia, former or current smoker, family history of CAD CAD = Coronary artery disease; OR = Odds Ratio, NA = not applicable

Table 4

Unadjusted and Adjusted Associations Between Epicardial and Paracardial Fat Volume Thresholds, Demographic/Clinical Risk Factors, and High-risk Plaque Features

Dependent Variable: Any High-risk Plaque Feature Independent Variables	Univariable Analysis		Multivariable Analysis <sup>b</sup> Model: EAT (indexed volume)		Multivariable Analysis <sup>b</sup> Model: PAT (indexed volume)	
	Unadjusted OR	p value	Adjusted OR	p value	Adjusted OR	p value
Indexed Epicardial Fat Volume (threshold 62.3 cc/m <sup>2</sup> )	2.50 (1.69–3.72)	<0.001	1.83 (1.10–3.05)	0.020	NA	NA
Indexed Paracardial Fat Volume (threshold 33.6 cc/m <sup>2</sup> )	4.12 (2.64–6.41)	<0.001	NA	NA	2.03 (1.15–3.59)	0.015
Age (years)	1.08 (1.05–1.10)	<0.001			1.03 (1.00–1.07)	0.087
Female	0.31 (0.21–0.46)	<0.001	0.42 (0.25–0.70)	0.001	0.45 (0.25–0.80)	0.007
No. of cardiovascular risk factors <sup>a</sup>	1.48 (1.24–1.76)	<0.001				
Coronary artery calcium score (log)	1.91 (1.71–2.13)	<0.001	1.75 (1.56–1.97)	<0.001	1.69 (1.49–1.91)	<0.001
Significant CAD (≥ 50% Stenosis)	23.31 (8.17–66.51)	<0.001	5.19 (1.64–16.41)	0.005	5.03 (1.54–16.47)	0.008

The summary is based on all 467 observations; 95% Confidence Intervals in brackets

<sup>a</sup>Risk factors include arterial hypertension, diabetes mellitus, dyslipidemia, former or current smoker, family history of CAD

<sup>b</sup>Stepwise regression approach including number of cardiovascular risk factors, age, sex and CTA findings, excluding variables  $p < 0.1$

CAD = Coronary artery disease; OR = Odds Ratio; NA = not applicable