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Cardiac CT for Quantification of Epicardial Fat: Where to Measure and Why?

Mohamed Marwan[1] **· Stephan Achenbach**[1]

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Abstract Epicardial adipose tissue has been attracting increasing attention over the last decade with a large body of evidence pointing towards significant associations between the volume of epicardial fat and atherosclerotic and non-atherosclerotic heart diseases. On the other hand, recent data from relatively large studies question the hypothesis of epicardial fat as an independent risk factor for atherosclerosis. This article reviews the available literature concerning imaging and quantification of epicardial adipose tissue and its potential clinical significance.

Keywords Epicardial · Cardiac CT · Pericardial · Paracardiac · Intrathoracic

Introduction

The term "epicardial adipose tissue" (EAT)—often called "epicardial fat"—refers to the visceral adipose tissue surrounding the heart and coronary arteries. Along with the pericardial fluid, epicardial adipose tissue creates a smooth surface that facilitates motion of the heart within the pericardium. It is worth mentioning that both the volume and the distribution of epicardial adipose tissue vary widely between individuals and do not show a strict correlation to body weight, body mass index, obesity, or the extent of abdominal visceral fat. Recently, the large body of evidence that has accumulated regarding a significant association between epicardial adipose tissue, risk factors for atherosclerosis, coronary artery disease, and cardiovascular events has led to an increased interest in the imaging and quantification of epicardial fat [1]. Furthermore, significant associations have been found between epicardial adipose tissue and non-atherosclerotic heart diseases, such as atrial fibrillation or left ventricular diastolic dysfunction [1, 2•].

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✉ Mohamed Marwan
mohamed.marwan@uk-erlangen.de

[1] Cardiology Department, University Hospital Erlangen, Erlangen, Germany

Fat Surrounding the Heart

The nomenclature used in the current literature to define adipose tissue surrounding the heart is heterogeneous and, to some extent, confusing. Terms such as "epicardial," "pericardial," "paracardiac," and "intrathoracic" fat have been used [1]. "Epicardial adipose tissue" (EAT) refers to the fat between the myocardium and the visceral layer of the pericardial sac, the serous epicardium. Although the term "pericardial fat" has been often used in the imaging literature to refer to adipose tissue enclosed within the pericardial sac, "epicardial adipose tissue" is more accurate. Paracardiac fat refers to fat situated outside the pericardium (Fig. 1).

Imaging Modalities for Quantification of Epicardial Adipose Tissue

Historically, several imaging modalities have been used to detect and quantify epicardial adipose tissue. These include echocardiography, magnetic resonance tomography (MRT), and computed tomography (CT). The advantage of completely covering the heart and thus providing true volume

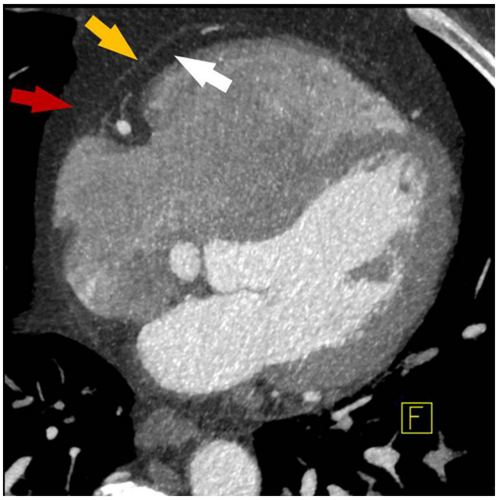

Fig. 1 Axial cross-section of a contrast-enhanced cardiac CT showing different fat depots surrounding the heart. *Orange arrow* points at the pericardial contour. *White arrow* points at the epicardial adipose tissue and the *red arrow* at the paracardiac fat. Reprinted with permission from the American College of Cardiology Cardiac Computed Tomography Self-Assessment Program (CCT-SAP 3)

measurements of epicardial fat has put more emphasis on CT as the modality of choice for quantifying epicardial fat. Surrogate imaging parameters to estimate the amount of epicardial fat include epicardial fat thickness, pericoronary fat thickness or volume, and epicardial fat areas in single cross-sections. However, due to the inter-individual differences in epicardial fat distribution, it is rather questionable to what extent such surrogate measures correlate with the absolute amount of epicardial adipose tissue.

Quantification of epicardial fat from cardiac CT is straightforward. CT has high spatial resolution, the full volume of the heart is covered in all routinely acquired cardiac scans, and fat has distinctly lower attenuation values compared to other tissue types (typically, less than −50 Hounsfield units (HU)). For quantification of epicardial fat volumes, both non-contrast and contrast-enhanced CT data sets have been used in scientific studies using available semi-automated software for quantification (Fig. 2). Typically, the user has to manually define the cranial and caudal boundaries of the heart and the pericardial sac is traced manually or automatically (with manual correction when necessary). Afterwards, a range of attenuation values is defined and any tissue within the traced pericardial sac that has a density within the predefined range of attenuation values is considered "epicardial fat." Selected attenuation thresholds in CT typically range from a lower value of −250 to –190 HU to an upper value between −50 and −30 HU [1]. For non-contrast CT, a typical fat attenuation range of −190 to −30 HU has been used. Very recently, Bucher et al. systematically compared the influence of technical parameters on epicardial fat volumes [3]. They observed significant differences in fat volumes measured in contrast and non-contrast studies when using the same upper threshold values. For contrast studies, an adjusted upper threshold value of −15 HU lead to better agreement when compared to measurements in native scans at an upper threshold of −45 HU. In previously published studies, processing times for epicardial fat measurement were reported to range from 5 to 11 min [1]. EAT volume measurements based on CT are highly reproducible with reported interobserver variabilities of 7, 8, and 15 % in three studies [1]. For semi-automated measurements of epicardial and thoracic fat from non-contrast CT, the interscan reproducibility has also been reported to be high, with correlation coefficients ≥0.98 between the two separate measurements [4].

Epicardial Fat: Do We Have Reference Values?

The absence of standardized reference values for what are to be considered as "normal" epicardial fat volumes represents a major obstacle for routine clinical use. In a community-based sample of more than 3000 middle-aged individuals, Thanassouslis et al. quantified epicardial and paracardiac fat volumes in participants from the Framingham Heart Study [5]. For the overall sample, the median values for epicardial fat volume were 117.5 and 93.9 cm^3, respectively, in men and women. They were 117.7 and 58.4 cm^3 for paracardiac fat. The authors defined abnormally high fat volumes on the basis of the age and gender-specific 90th percentiles for epicardial and paracardiac fat depots in a healthy reference sample (139.4 cm^3 in men and 119 cm^3 in women for epicardial fat and 150.5 and 73.3 cm^3 for paracardiac fat). Using these thresholds, 29.3 of men and 26.3 % of women with coronary artery disease had abnormally high epicardial fat volumes. In two studies, a simple threshold of 100 mm^3 for epicardial fat volume was used and higher epicardial fat volumes were associated with a significantly higher coronary artery calcium score and higher incidence of CAD [1]. In an outcome study, Cheng et al. used a threshold of 125 cm^3 and reported that epicardial fat volumes above that threshold were found more frequently in baseline CT scans of asymptomatic patients experiencing MACE on follow-up [6]. Tamarappoo et al. used the same threshold when comparing patients with myocardial ischemia by SPECT to controls [7]. Furthermore, Shmilovich et al. suggested indexing the volume of epicardial adipose tissue to the body surface area. In a healthy asymptomatic population of 226 subjects, they identified a value of 68.1 cm^3/m^2 as the 95th percentile threshold for abnormally high epicardial fat volume. They could show that values exceeding this threshold predicted major adverse cardiovascular events, with a trend to add to standard coronary calcium scoring and Framingham risk score in predicting cardiovascular events [8] (Fig. 3).

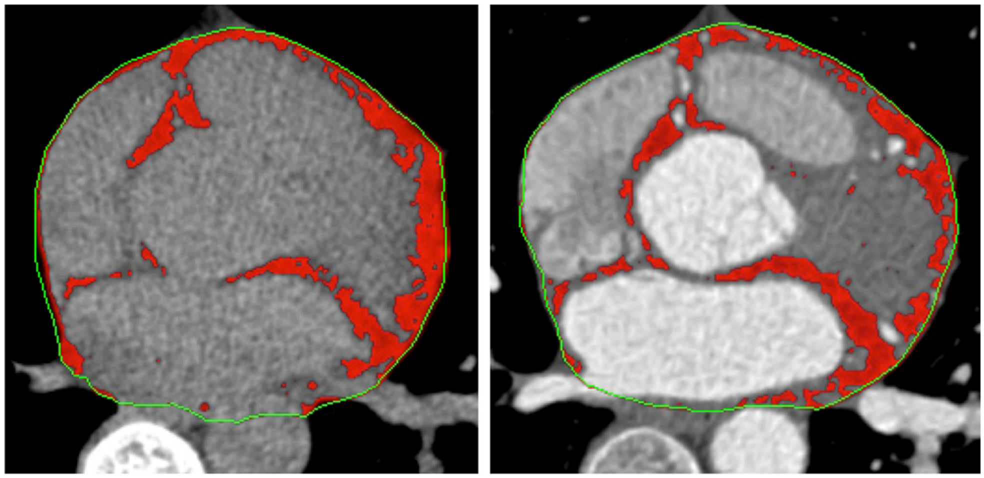

Fig. 2 Semiautomatic quantification of EAT with the help of dedicated software. The pericardial contour is identified with the *green line* and can be edited by the observer. EAT is shown in *red* (*left*: non-contrast CT and *right*: contrast-enhanced CT). Reprinted with permission from the American College of Cardiology Cardiac Computed Tomography Self-Assessment Program (CCT-SAP 3)

Association of Epicardial Adipose Tissue and Cardiovascular Morbidity

Epicardial Adipose Tissue and Atherosclerotic Coronary Artery Disease

Beyond serving as a mechanical buffer for cardiac motion and coronary artery distension, epicardial fat has been shown to exert direct metabolic and biochemical effects on the myocardium and coronary vessels. The anatomical, embryological, and biochemical diversity of adipose tissue enclosed within the pericardial sac compared other adipose tissues, such as paracardiac fat, subcutaneous fat, or visceral adipose tissue has triggered numerous hypotheses concerning specific metabolic properties of epicardial adipose tissue [1]. This inherent endocrine potential includes the secretion of several pro- and anti-inflammatory mediators and cytokines such as adiponectin, interleukin 6 (Il-6), and tumor necrosis factor (TNF) alpha1 [1, 9, 10]. An imbalance between pro- and anti-inflammatory mediators as well as cytokines secreted by epicardial adipose tissue is thought to contribute to a local influence on the embedded coronary arteries [1, 9, 10].

Numerous studies have shown a direct association between epicardial adipose tissue and established coronary artery disease. Specifically, several studies have reported a significant association between the presence and severity of coronary artery calcification and epicardial fat even after adjustment for traditional cardiovascular risk factors [1]. Furthermore, several studies have shown epicardial fat volume measured using CT to be significantly associated with the presence of any coronary plaque, non-stenotic plaques confirmed by coronary angiography, and non-calcified plaques [1, 11] [12]. Moreover, epicardial fat volume was found to be an independent predictor of coronary stenosis ≥70 % even after adjustment of traditional cardiovascular risk factors [13•]. Interestingly, a number of studies have reported a significant positive correlation between epicardial fat volume and progression of coronary artery calcification in intermediate-risk subjects and asymptomatic diabetics [1, 14].

On the other hand, some studies did not find an association between coronary atherosclerosis and epicardial fat volume. Very recently, investigators from the Young Finns Study could not find a significant association between pre-clinical athersclerosis determined by coronary artery calcification

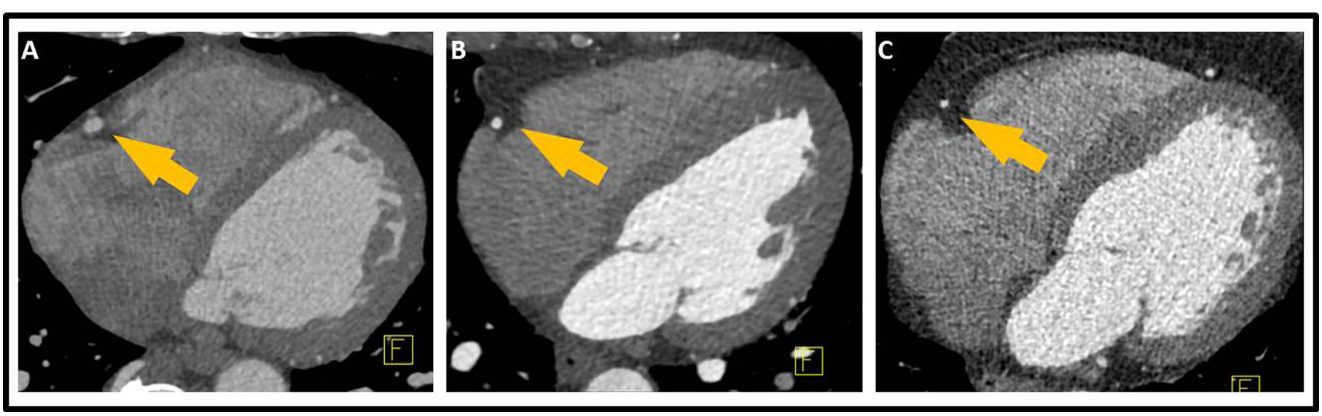

Fig. 3 Axial cross-section of contrast-enhanced CT at the level of the mid right coronary artery showing different amounts of EAT (**a** < **b** < **c**). Reprinted with permission from the American College of Cardiology Cardiac Computed Tomography Self-Assessment Program (CCT-SAP 3)

measured in native CT acquisitions and epicardial fat volume after adjustment for traditional risk factors. In their cohort, epicardial fat volume was most strongly associated with BMI and waist circumference [15••]. Along the same line, investigators from the CORE-320 multicenter trial in an analysis of 380 symptomatic patients did not find a significant association between the presence and extent of CAD as well as myocardial perfusion abnormalities identified by nuclear perfusion imaging on one hand and the volume of epicardial fat on the other hand [16••]. These data arising from relatively large populations add to the confusion concerning the clinical significance of epicardial fat quantification.

Epicardial Adipose Tissue and Acute Coronary Syndromes

Beyond established coronary artery disease, in a relatively large patient cohort, high epicardial fat volume (above 100 cm^3) was associated with vulnerable plaque components (non-calcified plaque, low density plaque, and positive remodelling) independent of obesity parameters (BMI and visceral adipose tissue) as well as coronary calcium score [17]. In a similar study by Harada et al., epicardial fat volume was significantly higher in patients with acute coronary syndromes compared to a control group of patients with normal coronary CT angiography, and a cut-off value of 100 ml was found to be independently associated with ACS in the multivariate analysis [18].

Epicardial Adipose Tissue and Cardiovascular Outcome: A Possible Link?

As compared to cross-sectional studies, prospective follow-up studies provide better validation for risk stratification methods. Previous relatively small studies have suggested a link between epicardial and intrathoracic fat volumes and the incidence of future adverse cardiovascular events [6, 19]. Recently, investigators of the Heinz Nixdorf Recall Study reported the association of epicardial fat volume, quantified from cardiac CT, with incident myocardial infarction in a European, population-based random cohort [20••]. The association of epicardial adipose tissue with coronary events was independent of traditional cardiovascular risk factors and remained statistically significant even after further adjustment for the coronary calcium score. This finding was partly explained by a stronger correlation between epicardial adipose tissue and incident events in subjects with low or no coronary calcium, which led the authors to conclude that quantification of epicardial adipose tissue from cardiac CT may complement prognostic information above coronary calcium scoring. However, in a population of subjects with acute chest pain, Forouzandeh et al. found an additional prognostic value of epicardial adipose tissue over coronary calcium only in subjects with calcium scores >400 [21]. Indeed, more data are needed to determine age- and gender-specific reference values to help clinicians interpret individual EAT volumes regarding their association with cardiovascular risk and their potential to identify symptomatic and asymptomatic subjects at increased risk who might benefit from a more intensive risk modification strategy.

Epicardial Adipose Tissue and non-Atherosclerotic Disease

The association of epicardial adipose tissue to cardiac disease is not limited to coronary atherosclerosis. Interestingly, a number of studies have indicated an association between epicardial adipose tissue and atrial fibrillation, which was suggested to be mediated by the inflammatory effects of epicardial fat [1, 22]. Moreover a potential relationship between epicardial adipose tissue and left ventricular diastolic dysfunction has been suggested [2•].

Conclusion

In summary, evidence is accumulating and suggests a potential causal relationship between the inherent metabolic characteristics of epicardial adipose tissue and coronary artery disease. Among available imaging modalities, computed tomography is the ideal imaging modality to accurately quantify the volume of epicardial adipose tissue, with this information already available (if measured) among the increasing numbers of cardiac and coronary CT investigations that are being performed for clinical reasons. Several limitations to the routine measurement of epicardial adipose tissue must be considered. First, there may be a coincidental co-localization of higher amounts of perivascular adipose tissue and the typical predilection sites of coronary atherosclerotic lesions or vulnerable plaque (such as the proximal left anterior descending coronary artery). Second, the clinical significance of quantifying epicardial fat warrants verification, especially with the emergence of data from large studies questioning its value as an independent risk factor for the presence and extent of CAD and the prediction of cardiovascular outcomes. Third, the best “threshold” to identify abnormally elevated epicardial fat volumes—probably somewhere around 100 cm^3—has not yet been identified. Finally, further data is needed to define the role of epicardial fat in guiding subsequent treatment decision; specifically, intensification or withholding of risk modifying measures. All the same, epicardial fat clearly seems to be more than just a substance to fill empty space, and further investigations will serve to clarify its intriguing association with coronary artery disease and other cardiac disorders.

Compliance with Ethics Guidelines

Conflict of Interest Mohamed Marwan and Stephan Achenbach declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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