

Epicardial adipose tissue: a simple marker of obesity or a complex mediator of cardiovascular disease?

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Abstract

Epicardial adipose tissue represents the layer of adipose tissue confined between the myocardium and visceral pericardium. Although for long its significance has remained unclear, there is now emerging evidence that suggests it is a potent marker of cardiovascular risk and is related to clinical outcomes. The current article reviews the anatomy and function of epicardial adipose tissue, the methods of its evaluation, its relationship to cardiovascular disease, and potential treatment strategies. ■ Heart Metab. 2014;63:13–17

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There has been an increase in obesity and diabetes mellitus in recent years and this has impacted the prevalence of additional metabolic and cardiovascular disorders.¹ Whereas subcutaneous adipose tissue (SAT) and visceral abdominal adipose tissue (VAT) have received much attention as potential culprits, epicardial adipose tissue (EAT) has largely been neglected. In the following review, we explore the increasing pathophysiological understanding of this intriguing fat depot over the last decade, and its potential contribution to cardiovascular disease.

Epicardial adipose tissue

There are two major types of adipose tissue, each with different physiological roles. White adipose tissue is predominantly located within the subcutaneous layers (SAT) and around the major organs (VAT). Here,

its primary function is to serve as a storage organ for triglycerides and free fatty acids during fasting, starvation, or exercise. Brown adipose tissue, on the other hand, is located in clusters around the clavicles, scapulae, and heart. It is a more metabolically active fat depot and contains numerous mitochondria that confer to it a thermogenic capability.

Epicardial adipose tissue is brown adipose tissue and is located between the myocardium and the visceral pericardium. It constitutes 20% of the heart's mass while covering 80% of its surface.^{2,3} In the nonobese state, EAT is likely to have a number of beneficial effects. As a reservoir of free fatty acids, it has the potential to provide an energy source for the myocardium when metabolic requirements are high and to serve as a buffer for high circulating fatty acid levels.⁴ Epicardial fat is also known to secrete adiponectin and adrenomedullin, which

Abbreviations

BMI: body mass index; **CACS:** coronary artery calcium score; **CAD:** coronary artery disease; **EAT:** epicardial adipose tissue; **SAT:** subcutaneous adipose tissue; **VAT:** visceral adipose tissue

are known to have important anti-inflammatory and anti-atherogenic effects. Finally, the EAT layer may provide cushioning for the coronary arteries and reduce torsional forces.

Imaging modalities

EAT can be measured by echocardiography, computed tomography, and cardiac magnetic resonance imaging (CMRI). On 2-dimensional transthoracic echocardiography, epicardial fat can be best visualized in the parasternal long-axis and short-axis views as an echo free space between the myocardium and visceral layer of the pericardium. In the parasternal long-axis plane, using the aortic annulus as a landmark, its thickness is usually measured perpendicularly to the right ventricular free wall of the right ventricle at end systole in three cardiac cycles.⁵ End-systolic measurements are preferable to diastolic measurements owing to compression of EAT during systole. If the amount of EAT is large (>15 mm), then the appearance may be echogenic in nature, which may aid in distinguishing it from a significant pericardial effusion.

One of the difficulties with the incorporation of echocardiographic EAT measurements into clinical practice is the lack of appropriate normal ranges. There is a wide variation in EAT measurements from a minimum of 1 mm to a maximum of 23 mm that reflects the wide variation in abdominal adipose tissue deposits among patients undergoing routine echocardiography.⁶ Of the few studies that have been performed, it has been shown that a 6 to 7 mm rim of EAT tissue most likely represents a normal range for men and women undergoing routine echocardiograms. For the prediction of a metabolic syndrome, a threshold of 9.5 mm for men and 7.5 mm for women has been proposed.⁶

In general, cardiac computed tomography has superseded echocardiography as the technique of choice for the accurate quantification of EAT owing to its high spatial resolution and reproducibility. The volume of EAT can be calculated by identifying the

superior and inferior boundaries of the pericardium and then tracing around the parietal pericardium using 5 to 10 control points in sequential axial views. From these points, a dedicated software is able to generate a smooth and closed pericardial contour. Epicardial fat volume is then calculated by summing the contiguous 3-dimensional voxels that occur within the Hounsfield Units (HU) range for adipose tissue (-190 and -30 HU; *Figure 1*).⁷

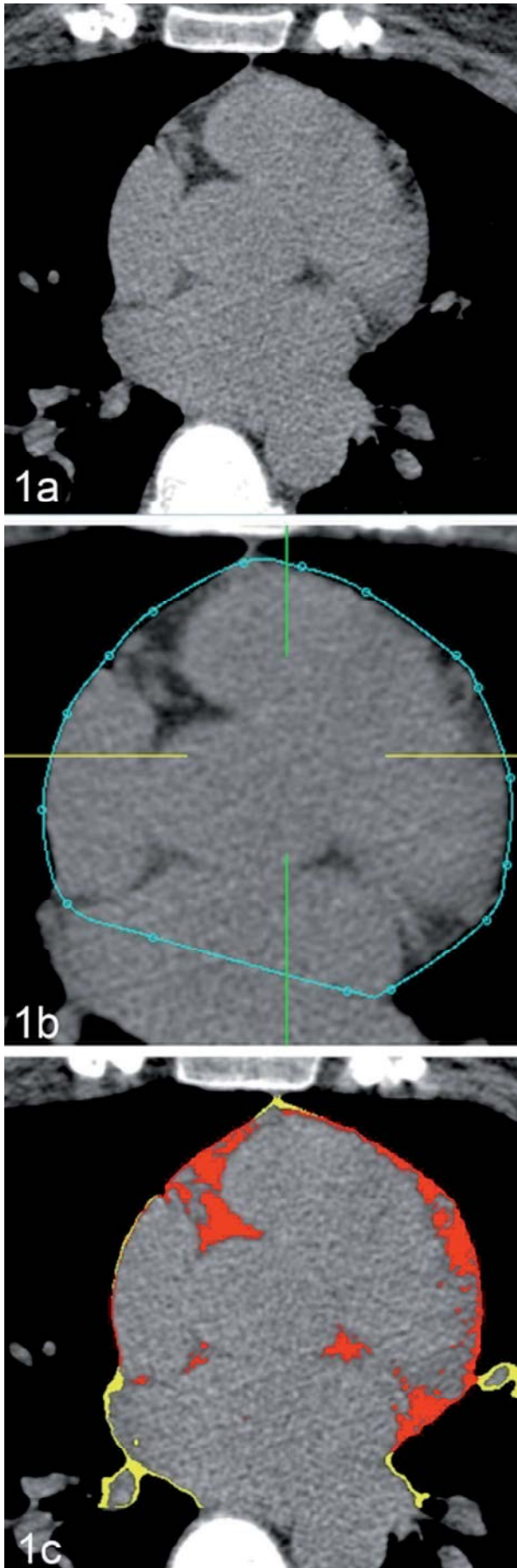
CMRI also has the capability to measure epicardial adipose tissue thickness anterior to the epicardial surface on the right ventricular free wall on the horizontal long-axis, 4-chamber, and short-axis views.⁸ Tracing around the epicardial fat on serial short-axis slices can also quantify the absolute amount of epicardial fat.⁹

Potential mechanisms of cardiovascular disease

In obesity, diabetes, metabolic syndrome, and hypertension, the protective effects of EAT are overcome by its ability to promote vascular dysfunction and atherogenesis.¹⁰ An expansion of EAT occurs, which is accompanied by tissue hypoxia and an infiltration of macrophages and T cells. This reduces the production of protective adipokines such as adrenomedullin and adiponectin,¹¹ and increases the production of detrimental cytokines such as leptin, resistin, chemerin, interleukin-6, and tumor necrosis factor α (TNF- α).¹² Adiponectin expression from EAT has been shown to be lower in patients with coronary artery disease (CAD) compared with patients without CAD,^{11,13} whereas proinflammatory cytokines are higher in samples of EAT taken from patients with CAD, relative to SAT.¹⁴ These findings have led investigators to propose that EAT may exert its biological effect by a local paracrine or vasocrine effect on the adjacent myocardium and coronary vasculature.¹⁵

Atherosclerosis

Primary evidence supporting a pathogenic role of EAT in cardiovascular disease is its association with coronary atherosclerosis.^{7,16} In the Framingham Heart Study,¹⁶ Rosito et al demonstrated, in 1155 patients, an independent relationship of epicardial fat volume to coronary calcium after adjustment for conventional cardiovascular risk factors, body mass index (BMI), and waist circumference. Similarly, in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) Registry,



Dey et al showed in 201 healthy asymptomatic individuals that EAT was independently associated with coronary calcium.⁷ A number of additional studies have also shown a relationship of EAT with the extent and severity of CAD angiographically,¹⁷ and plaque morphology,¹⁸ progression,¹⁹ and vulnerable plaque features.^{18,20}

Myocardial and arrhythmic heart disease

In addition to its association with atherosclerotic coronary disease, EAT has also been implicated in other cardiovascular disease states. In a study of 273 patients, Al Chekatie et al demonstrated increased epicardial fat volume in 197 patients with persistent or paroxysmal atrial fibrillation when compared with 76 patients in sinus rhythm.²¹ This relationship was independent of diabetes mellitus, hypertension, left atrial size, and BMI and suggests that EAT may have a direct pathogenetic effect on left atrial myocardium.²² Other studies have also shown associations of EAT with diastolic function abnormalities²³ and also left ventricular structural and functional changes.²⁴

Prognostic value

A number of studies have demonstrated that EAT may be an important prognostic marker of cardiovascular events. Cheng et al compared epicardial fat volume (EFV) between 58 patients who developed major adverse cardiac events with 174 propensity-matched controls. The authors observed higher EFV for those patients who developed major adverse coronary events (MACE) when compared with event-free controls with similar cardiovascular risk profiles.²⁵ In another study of 760 patients with acute chest pain, all of whom underwent coronary computed tomography, Forouzandeh et al investigated whether EAT improved risk stratification beyond calcium scoring.²⁶ The authors showed that both coronary artery calcium stores (CACS) and EAT were independently associated with MACE in patients with chest pain

Fig. 1 Epicardial fat volume measurement using the QFAT software (Cedars-Sinai Medical Center, Los Angeles, California). **1a.** Shows a noncontrast enhanced cardiac computed tomographic scan of the chest. **1b.** The pericardium is marked on serial slices from the branching of the main pulmonary to the inferior aspect of the heart where the posterior descending artery is first seen within the inferior atrioventricular groove. **1c.** The QFAT software then automatically calculates the volume of epicardial adipose tissue within the visceral pericardium as those voxels with a Hounsfield Unit (HU) value ranging from 190 to 30 HU (red). Transthoracic fat is calculated as adipose tissue outside of the pericardium and is marked as yellow.

and that EAT may have added value in patients with a CACS >400 Agatston units. Finally, Mahabadi et al studied 4093 participants from the Heinz Nixdorf Recall Study and investigated whether quartiles of EFV were related to incident coronary events.²⁷ The authors showed that coronary events increased with each quartile increase of EAT and that a doubling of EAT was associated with a 1.5-fold increase for coronary events, even after adjusting for conventional cardiovascular risk factors and CACS.

Modifying epicardial fat: lifestyle, weight reduction, and pharmacotherapy

Given the association of EAT with cardiovascular disease and clinical outcomes, there have been a number of studies that have attempted to reduce its quantity. In an observational study of 374 healthy asymptomatic individuals, Nakazato et al showed that $\geq 5\%$ weight change resulted in EFV changes.²⁸ Iacobellis et al introduced a severe calorie restriction program (900 kcal/day) to 20 subjects with severe obesity.²⁹ At six months there was a 20% reduction in body weight, 19% reduction in BMI, 23% reduction in waist circumference, and 32% reduction in epicardial fat measured echocardiographically. Kim et al studied the effects of exercise training without calorie restriction on 24 obese middle-aged men.³⁰ Following a 12-week supervised exercise training program there was a significant decrease in epicardial fat thickness measured over the right ventricular free wall on echocardiography. This change was greater than that of the initial waist circumference, BMI, and weight, and was independently related to changes in visceral adipose tissue and systolic blood pressure. Similar findings have also been demonstrated in patients undergoing bariatric surgery for severe obesity. Iacobellis et al showed a mean reduction of 23% in echocardiographically measured fat thickness at 8 months in 23 patients who underwent bariatric surgery.⁶ Gaborit et al showed using ¹H magnetic resonance spectroscopy³¹ that bariatric surgery resulted in substantial weight loss in a study of 23 patients and that this was accompanied by a reduction in insulin resistance parameters, an improvement in cardiac function parameters, and a significant reduction in epicardial fat volume. Finally, Schinkel et al showed significant changes in epicardial fat upon MRI in 10 morbidly obese patients with type 2 diabetes within 16 weeks following gastric bypass surgery.³²

There have been limited studies investigating the use of medication on epicardial adipose tissue. In a substudy of the BELLES trial (Beyond Endorsed Lipid Lowering with Electron Beam Tomography Scanning), Alexopoulos et al studied the effects of 80 mg/day of atorvastatin versus pravastatin 40 mg/day for one year in postmenopausal women.³³ The authors showed greater EAT regression (-3.4%) with atorvastatin than in the pravastatin treated arm (-0.83%), which suggests that higher intensity statins may confer a beneficial effect on epicardial fat (potentially by their anti-inflammatory effect).

Conclusions

Over the last decade our understanding of the physiological function and pathological effects of EAT have increased substantially. Studies indicate that EAT is likely to represent a useful cardiovascular risk marker and one that has the ability to potentiate a variety of different cardiovascular disease states and affect the clinical outcome. The modulation of EAT volume using various lifestyle interventions and pharmacotherapy to manage potential cardiovascular complications shows promise, however, further outcome data is required prior to their widespread recommendation. ■

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