

# Cardiac Adiposity and Cardiovascular Risk: Potential Role of Epicardial Adipose Tissue

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**Abstract:** Emerging evidence suggests that cardiac adiposity may play an important role in the development of an unfavorable cardiovascular risk profile. The concept of adiposity of the heart, as new cardiovascular risk factor and marker, is rapidly emerging. Recent papers suggest that epicardial fat, an index of cardiac visceral adiposity could locally modulate the morphology and function of the heart. The close anatomical relationship between epicardial adipose tissue and the adjacent myocardium should readily allow local paracrine interactions between these tissues. Epicardial fat may play a functional and mechanical role in left ventricular hypertrophy, atrial dilatation or diastolic dysfunction. Echocardiography has been recently proposed for the direct assessment of epicardial adipose tissue. Echocardiographic assessment of epicardial fat may be a helpful tool not only for diagnostic purposes, as marker of visceral adiposity and inflammation, but also for therapeutic interventions with weight reduction drugs or pharmaceuticals targeted to adipose tissue. Nevertheless the subject is in its infancy and further studies are needed. In fact it is difficult to determine whether epicardial fat has a direct pathogenic role in the development of cardiac changes. It also remains to be determined whether this location of fat is physiologically or pathologically important and whether it can be used to replace abdominal obesity, or its surrogate marker, waist circumference, as a cardiovascular risk factor.

In this article, epicardial adipose tissue's structure, function, method of assessment and reliability as a marker of visceral and cardiac adiposity is briefly reviewed.

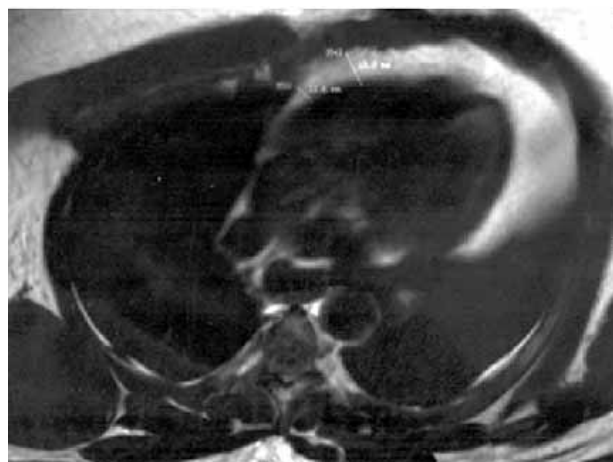
**Key Words:** Epicardial adipose tissue, epicardial fat, cardiac adiposity, echocardiography.

## INTRODUCTION

Morbid obesity is associated with cardiovascular disease [1]. Compelling evidence also showed that adipose tissue act as endocrine, secretory organ [2]. Since blood vessels express receptors for most of the adipocyte-derived factors, adipose tissue seems to play a key role in cardiovascular physiology through paracrine, and endocrine mechanisms [2].

Visceral adipose tissue, the fat that surrounds the internal organs in the cavities of the body seems to predict unfavorable cardiovascular and metabolic risk profile more than total adiposity [3]. Some studies emphasized the potential importance of the anatomical closeness of some visceral adipose tissues depots to target organs, as well as the heart [4]. The concept of cardiac adiposity, as new cardiovascular risk factor and marker is rapidly emerging [5]. Recent evidences suggest that cardiac adiposity could locally modulate the morphology and function of the heart and work as easy and reliable biomarker and therapeutic target [4-5].

A significant interest lies in studying and reliably quantifying adipose tissue [6]. Magnetic resonance imaging (MRI) is the gold standard technique to accurately measure subcutaneous, visceral and therefore cardiac adiposity (Fig. 1) [7]. Several MRI techniques and automatic or semi-automated analysis of VAT have been proposed and applied [6]. MRI is



**Fig. (1).** MRI appearance of epicardial adipose tissue.

Epicardial adipose tissue appears as T1-emphasized high signal density on the free wall of right ventricle and around the left ventricular apex. TSET1-weighted sequence with oblique axial orientation, 10-mm thickness section with 1-mm intersection gap, 370 FOV, 256 x 256 matrix.

becoming more readily available, both for research and clinical application, and is not much more expensive than other diagnostic procedures. However, Iacobellis *et al.* proposed the direct measurement of epicardial adipose tissue thickness via echocardiography as marker for cardiac adiposity (Fig. 2) [8]. Epicardial fat can be readily quantified during routine echocardiography, which is widely available and commonly used to diagnose and monitor a variety of heart diseases.

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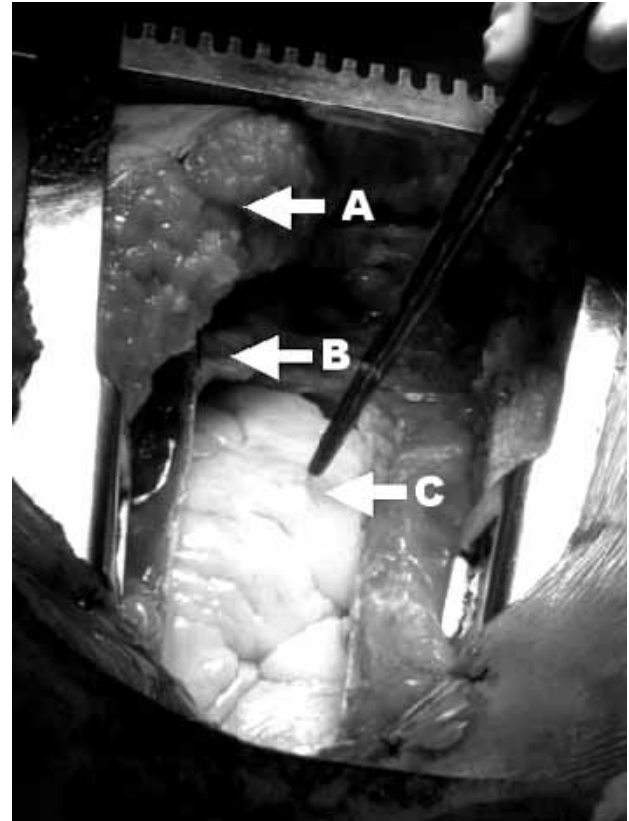
**Fig. (2).** Echocardiographic appearance of epicardial adipose tissue. Transthoracic echocardiogram showing a large area of epicardial adipose tissue (arrows) on free wall of right ventricle.

In this article, we review epicardial adipose tissue's basic characteristics, method of clinical assessment and reliability in measuring visceral and cardiac adiposity.

#### EPICARDIAL ADIPOSE TISSUE AS ENDOCRINE ORGAN

Epicardial adipose tissue is the visceral fat located around the heart (Fig. 3). Epicardial adipose tissue is suspected to directly interact with the myocardial tissue. In fact, both tissues share the same coronary blood supply and no fascia like structure separates the epicardial adipose tissue from myocardium [4]. The specific function of epicardial adipose tissue is still unclear. Interestingly, the tissue does not exist in laboratory mice or rats [9]. Marchington's animal experimental studies showed that the principle difference between epicardial adipose tissue and other visceral adipose tissues is its greater capacity for free fatty acid release [9]. Epicardial adipose tissue may act as a local energy supply for the myocardium or buffer against toxic levels of free fatty acids [9].

Biomolecular studies in humans showed that epicardial fat tissue is clearly metabolically active and an important source of both pro (tumor necrosis factor- $\alpha$ , interleukin 1, interleukin 6, nerve growth factor) and anti (adiponectin) inflammatory adipokines which might significantly affect cardiac function and morphology [10-13]. Recently, proinflammatory cytokines production from epicardial adipose tissue in cardiac surgery patients has been related to the development of postoperative insulin resistance [14]. Macrophage infiltration into epicardial fat has also been found in subjects with coronary artery disease, suggesting a condition of chronic inflammation in this small cardiac fat depot [11]. Epicardial CD45 expression was also significantly higher than omental adipose tissue indicating significant infiltration of macrophages [12]. Several mechanisms could be evoked to explain the inflammatory cytokine production from epicardial adipose tissue. The regional ischemia and depressed myocardial function, as well as that observed in sub-



**Fig. (3).** Epicardial adipose tissue in a patient with coronary artery disease undergoing a triple coronary artery bypass.

(A) Adipose tissue deposited in the chest under the skin (subcutaneous). (B) Pericardial tissue. (C) Epicardial adipose tissue pulled up by forceps (the adipose tissue abnormally covers entire heart in this patient).

jects with coronary artery disease, with the subsequent increase in the redox state and cytokine expression, could active visceral adipose tissue oxidant-sensitive inflammatory signals in adjacent adipose stores [11]. <http://circ.ahajournals.org/cgi/content/full/108/20/-R21-138301> The presence of inflammatory cells in adipose tissue could also reflect the response to plaque rupture, analogous to inflammatory infiltrates in the adventitia and perivascular region adjacent to advanced atherosclerotic lesions. <http://circ.ahajournals.org/cgi/content/full/108/20/-R24-138301> One could also hypothesize a role for periadventitial-paracrine processes. Thus, increased concentrations of inflammatory mediators such as TNF- $\alpha$  in the tissues surrounding human epicardial coronary arteries could lead to amplification of vascular inflammation, plaque instability *via* apoptosis and neovascularization [11].

Of note is our previous observation that adiponectin expression is significantly higher in epicardial fat isolated from subjects with normal coronary arteries than in patients with severe coronary artery disease [10]. Thus epicardial fat could also exert favourable effects on the adjacent coronary artery through increased adiponectin production. Taken together these observations would suggest both favourable and unfavourable effects of epicardial fat through the paracrine pro-

duction of adipokines [9-14]. Although the potential mechanisms are still unclear, an imbalance in the production of anti and pro-inflammatory factors from epicardial fat may play a role in cardiac abnormalities [10].

### EPICARDIAL ADIPOSE TISSUE AND LEFT VENTRICULAR MORPHOLOGY

Increase in epicardial adipose tissue seems to be associated with abnormal cardiac morphology. Previous studies showed that epicardial adipose tissue is associated with increased ventricular mass [15-16]. Increased left ventricular [LV] mass is a well-recognized independent cardiovascular risk factor. Hypertrophy is a compensatory remodelling of the left ventricle in response to a pressure or a volume overload and the combined effect of metabolic and neurohormonal factors. The role of cardiac adipose tissue in inducing changes in LV geometry has been recently explored. Autopsy [15] and echocardiographic [16] findings strongly suggest that an increase in LV hypertrophy is associated with a consensual and proportional increase in epicardial adipose mass. The presence of excessive epicardial fat adds to the weight of the ventricles and increases the effort involved in pumping blood around the body. In fact, LV fat weights are significantly greater in hypertrophic human hearts and the epicardial fat located over both ventricles accounted for around 20% of total ventricular mass. The positive relationship between the amount of epicardial mass and LV mass was also recently reported in echocardiographic studies [16]. Epicardial fat thickness was the best correlate ( $R^2=0.39$ ,  $p<0.01$ ) of LV mass in subjects with a wide range of adiposity [16]. Epicardial adipose tissue thickness is also associated with right ventricle mass, as echocardiographic studies in obese subjects recently reported [17]. Although, the mechanisms underlying the relationship between ventricular morphology and epicardial fat are still not completely understood, local functional and mechanical regulation can be postulated. Adipose and muscular component of the heart share the same coronary blood supply and no structures resembling a fascia separate the adipose and myocardial layers [4]. Given the active role of epicardial adipose tissue in synthesizing and releasing into the bloodstream a number of peptides, a paracrine effect of epicardial fat on LV through local production of adipokines is not unlikely. The cardiac fat pad could also mechanically affect cardiac work and consequently induce hypertrophy as compensatory response. The amount of epicardial fat is also significantly related to insulin resistance and glucose intolerance in obese subjects [18], suggesting a possible combined unfavorable effect of impaired insulin sensitivity and increased epicardial fat on LV mass and function. A recent study also demonstrates that atria enlargement and impairment in diastolic filling is associated with epicardial adipose tissue in morbidly obese subjects [17].

### ECHOCARDIOGRAPHIC EPICARDIAL ADIPOSE TISSUE AS RISK MARKER

Echocardiography is non-invasive and safe. It is also relatively cost and time efficient since it is usually part of the routine assessment in patients with suspected cardiovascular risk. Recent studies have demonstrated the reliability of epicardial adipose tissue's thickness measurement *via* echo-

cardiography as a marker for visceral adiposity and adiposity-related metabolic and cardiovascular risk [8,19].

Epicardial fat thickness is measured on the free wall of the right ventricle from both parasternal long- and short-axis views (Fig. 2) [8]. The largest amount of epicardial fat is usually seen at this right ventricular free wall site. Epicardial adipose tissue is usually seen as an echo-free or if it is massive as hyper echoic space. It is important to ensure that epicardial fat thickness is not measured obliquely.

Epicardial adipose tissue has been shown to be very closely related to intra-abdominal adiposity, a marker of entire body visceral adiposity, according to various magnetic resonance imaging studies [8,19]. An excellent correlation between epicardial adipose tissue and waist circumference ( $r = 0.895$ ,  $p = 0.01$ ) and magnetic resonance image abdominal visceral adipose tissue ( $r = 0.864$ ,  $p = 0.01$ ) is reported [8]. Bland-Altman plot also showed the good agreement between echocardiographic and MRI measurements [8]. In the same study, multiple regression analysis proved that epicardial adipose tissue thickness was the strongest independent variable correlated to magnetic resonance image visceral adipose tissue ( $r^2 = 0.442$ ,  $p = 0.02$ ) [8].

Echocardiographic epicardial fat thickness has been shown to be directly associated with many of metabolic syndrome features as well as increased LDL cholesterol, fasting insulin ( $r^2 = 0.387$ ;  $p = 0.03$ ), left ventricular mass ( $r = 0.75$ ing,  $p = 0.01$ ) and diastolic blood pressure ( $r^2 = 0.387$ ;  $p = 0.02$ ), and decreased adiponectin [19].

The fact that epicardial adipose tissue measurement is not confounded by subcutaneous fat should be also considered. Given the important difference between visceral adiposity and peripheral adiposity in the development of cardiac modifications and cardiovascular diseases, the accurateness of this echocardiographic measurement seems to be remarkable [20-22]. Waist-circumference is now widely used as surrogate indicator of visceral adiposity. Nevertheless it is confounded by subcutaneous abdominal fat thickness mostly in severely obese subjects. Thus, given the poor sensitivity and specificity of waist circumference as a measure of visceral adiposity, echocardiographic measurement of visceral adipose tissue could provide a more accurate visceral fat content estimate. However, whether it can be used to replace waist circumference as marker of visceral obesity remains to be demonstrated.

### FUTURE PERSPECTIVES

There is a compelling need to quantify visceral adipose tissue not only for diagnostic purposes, but also for therapeutic interventions with weight reduction drugs or pharmaceuticals targeted to adipose tissue, as well as hormone replacement therapy [23], glitazones, fibrates, sartans, highly active antiretroviral therapy and anti-obesity medications. Interventional studies seem to be warranted in this direction. It should be also of potential great interest to evaluate the specificity of epicardial adipose tissue measurement in subjects without increased visceral adiposity, but manifest cardiovascular diseases. The fact that the epicardial adipose tissue is a source of pro and anti inflammatory cytokines could make it as a possible marker of inflammation in pa-

tients with coronary artery disease. Since we know that ethnicity differently correlates with cardiovascular risk and regional fat distribution, echocardiographic assessment of cardiac fat could be also of interest in multiethnic population studies. Although, the epicardial adipose tissue measurement *via* echocardiography technique to predict visceral and cardiac adiposity and their associated health risks is relatively young, it may have the potential to be considered a reliable and easy diagnostic tool and an effective therapeutic target.

## CONCLUSIONS

Growing evidences suggest that epicardial fat, an index of cardiac visceral adiposity could locally modulate the morphology and function of the heart. The close anatomical relationship between epicardial adipose tissue and the adjacent myocardium should readily allow local paracrine interactions between these tissues. Epicardial fat may play a functional and mechanical role in left ventricular hypertrophy, atrial dilatation or diastolic dysfunction. Nevertheless the subject is in its infancy and further studies are needed. In fact it is difficult to determine whether epicardial fat has a direct pathogenic role in the development of cardiac changes. It also remains to be determined whether this location of fat is physiologically or pathologically important and whether it can be used to replace abdominal obesity, or its surrogate marker, waist circumference, as a cardiovascular risk factor.

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