Heart Failure and Epicardial Adipose Tissue

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Gianluca Iacobellis

Key Points

- Epicardial adipose tissue plays a pathogenic role in heart failure. Thermogenic, paracrine, and neural factors seem to be involved.
- Epicardial fat volume is higher in subjects with both systolic and diastolic heart failure.
- Epicardial fat can be reduced in patients with severe heart failure due to fibrotic and apoptotic changes.

Introduction

Heart failure (HF) is a complex clinical syndrome that results from both structural and functional impairment of ventricular pump or filling. The causes leading to HF are multiple, and often co-occurring, such as coronary artery disease (CAD), atrial fibrillation (AF), preexisting cardiomyopathies, myocarditis, metabolic disorders, and acute organ failure. Heart failure can be classified into two types according to the left ventricular ejection fraction (reduced or preserved): systolic heart failure with reduced ejection fraction (HFrEF), and diastolic heart failure with preserved ejection fraction (HFpEF) [1].

Epicardial adipose tissue (EAT) has been investigated in patients with heart failure and suggested to play a pathogenic role. Given its peculiar location and intense metabolic activity, it is plausible to see the role of EAT in the development and progression of EAT. Also, abnormal or excessive EAT has shown to be correlated with both systolic and diastolic functions. Hence, it would be logical to attribute some action of EAT in affecting either the left ventricular pump or the filling phase. However, the results are quite scarce and controversial, also due to the occurrence of other conditions that can affect EAT. Hence, the role of EAT in independently causing or contributing to the development of HF is still uncertain.

Thermogenic Epicardial Fat and Heart Failure

EAT displays genetic and functional features similar to those of the brown fat [2]. Human EAT has the potential to serve as a thermogenic source for the myocardium and therefore protect it against hypothermia. A recent study found that patients with HFrEF expressed significantly lower thermogenic genes in EAT than those

G. Iacobellis (✉)
Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL, USA
e-mail: giacobellis@med.miami.edu

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with HFpEF [3]. In fact, uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), and PR-domain-missing 16 (PRDM16) expression were significantly lower in EAT of patients with HRrEF than those with HFpEF. The correlation of EAT brown fat genes with HF was not independent. In fact, age, male gender, and different cardiovascular diseases were also associated with the levels of thermogenic genes expression. This study suggests that an adequate expression of thermogenic genes could serve a possible protective factor against congestive heart failure. Consequently, a loss of functional EAT brown-like features would contribute to the development of HFrEF. This hypothesis seems to be confirmed by another study in both mice and humans with obesity and heart failure [4]. The authors suggested a role of the epicardial fat heme oxygenase-1 (HO1) PGC-1α in modulating the left ventricle function. HO-1 PGC-1α and PRDM16 were inversely correlated with left ventricular ejection fraction. In summary, these studies suggest a potential protective role of the brown fat features of EAT against systolic heart failure. EAT thermogenic genes could serve as a therapeutic target in patients with HFrEF. Pharmacological manipulation would be certainly challenging as EAT brown fat-like properties tend to significantly decrease with aging [5]. However, these findings should be confirmed in larger and multicenter research trials.

Epicardial Fat Adipokines and Heart Failure

EAT is an active paracrine and endocrine organ. EAT secretome is large and includes both pro- and anti-inflammatory adipokines. Among these, EAT adiponectin has shown to provide potential cardioprotective effects. EAT adiponectin expression is downregulated in patients with coronary artery disease [6]. In a study with patients undergoing cardiac surgery, p53 and adiponectin mRNA expression was measured in frozen fat biopsies or explants culture from both EAT and subcutaneous fat (SAT). p53 expression in adipose tissue is involved in the development of insulin resistance and inflammation [7]. Higher p53 expression was linked to increased production of pro-inflammatory cytokines. p53 mRNA expression levels were higher in EAT of HF patients as compared to SAT. p53 was inversely correlated with adiponectin and regulated by sympathetic activation pathway in patients with HF. A neuromodulatory role of EAT in heart failure will be discussed in details in chap. 12.

Epicardial Fat in Diastolic and Systolic Heart Failure

The relationship between EAT and HF was evaluated by a number of studies, although few of these were focused to specifically address it. In these studies, populations were quite heterogeneous with patients with or without coronary artery disease (CAD) and other confounding factors such as diabetes and hypertension. The role of EAT in the development or progression of HF can be better interpreted if results are adjusted by these factors, and diastolic and systolic functions are factored in the relation. A recent meta-analysis included 26 studies accounting for more than 4000 patients [8]. This analysis was conducted on the basis of diagnosis of left ventricular diastolic and systolic dysfunction and their correlation with EAT. Left ventricular diastolic dysfunction (LVDD) was defined echocardiographically by a ratio of early mitral valve flow velocity (*E*) to early diastolic lengthening velocity (*e′*; *E*/*e′*) during tissue Doppler imaging of ≥10; left ventricular systolic dysfunction (LVSD) was defined with ejection fraction (LVEF) ≤50%. Patients with preserved systolic function (HFpEF) are those with LVDD, whereas those with reduced systolic function (HFrEF) are presenting with LVSD. As previously discussed, EAT can be measured either with standard echocardiography or CT or CMR, as

thickness or volume, respectively. The relationship between ultrasound measured EAT thickness and LVDD was reported in eight studies that included 775 cardiac patients with LVDD and 695 controls without LVDD [9–15]. Overall, EAT thickness was significantly higher in patients with LVDD as compared to those without it. The relationship between EAT volume and LVDD was investigated in six studies that included 433 cardiac patients with LVDD and 272 controls without LVDD [16–20]. Overall, EAT volume in cardiac patients with LVDD was increased compared to those without LVDD. One study measured EAT volume with cardiac magnetic resonance in patients with HFpEF defined by an LVEF >40% [21]. EAT volume was significantly higher in HFpEF patients compared to controls (107 mL/m^2 vs. 77 mL/m^2, $P < 0.0001$), despite similar body mass index. HF patients with atrial fibrillation and/or type 2 diabetes mellitus had higher EAT than HF patients without these comorbidities. We can conclude that EAT is higher in patients with LVDD as compared to patients without LVDD, irrespective of whether is measured as volume or thickness. Hence, diastolic heart failure is more commonly associated with increased EAT.

The role of EAT in systolic heart failure (HFrEF) is less consistent, as findings are actually quite conflicting. The association between EAT and LV function was evaluated using either CMR or echocardiography. In some studies, EAT was found higher in subjects with LVSD [22–25]. One study showed that patients with HFrEF had significantly higher indexed EAT volume as measured with cardiac magnetic resonance imaging when compared with patients with HFpEF or the control group [22]. Another study reported an association between EAT and global longitudinal strain, a subclinical measure of myocardial function [23]. An independent correlation between echocardiographic EAT thickness and LVEF was also observed [24]. Epicardial fat thickness is associated with the severity of HF in patients with nonischemic dilated cardiomyopathy [25]. In fact, patients with HF had significantly lower epicardial fat thickness than those in the control group. Some of these results may be confounded by the co-occurrence of diabetes or CAD or obesity. Mechanical restriction from excessive EAT during the diastole may affect the ventricular filling and, consequently, reduce cardiac output in obese subjects [25].

However, some other studies found opposite results. Doesch et al. reported a reduced EAT in patients with congestive, HFrEF [26–28]. When EAT was adjusted by LV end-diastolic mass was significantly reduced in patients with severe HF (EF < 35%) compared to healthy controls (Fig. 11.1). In the analysis performed by Doesch and colleagues, the reduction of EAT was irrespective of the underlying cause of the cardiomyopathy [26]. In fact, there were no differences in EAT between patients with or without CAD. Doesch attributes the reverse correlation between LVEF and indexed EAT to the left ventricular remodeling occurring in heart failure. Lower EAT in patients with poor systolic function was also confirmed in another study [24]. EAT volume, as measured with cardiac magnetic resonance, was also found to be significantly lower in obese patients with HFpEF, and no correlation between EAT and EF was observed [29].

EAT thickness, as measured according to the method first described by Iacobellis et al. [33, 30], was also found to be lower in subjects with HFrEF (EF < 50%) as compared to those without HF, independent of atrial fibrillation and HF [31]. Some mechanisms can be evoked to explain these findings. Epicardial fat reduction in HF subjects may reflect the overall fat mass reduction, commonly observed in these patients. It is also possible to hypothesize that epicardial fat pad may incur in fibrotic changes during chronic cardiac failure [32]. However, the exact interaction of EAT and HF is still unclear. Whether EAT plays a role in the long-term prognosis of HF requires future investigation.

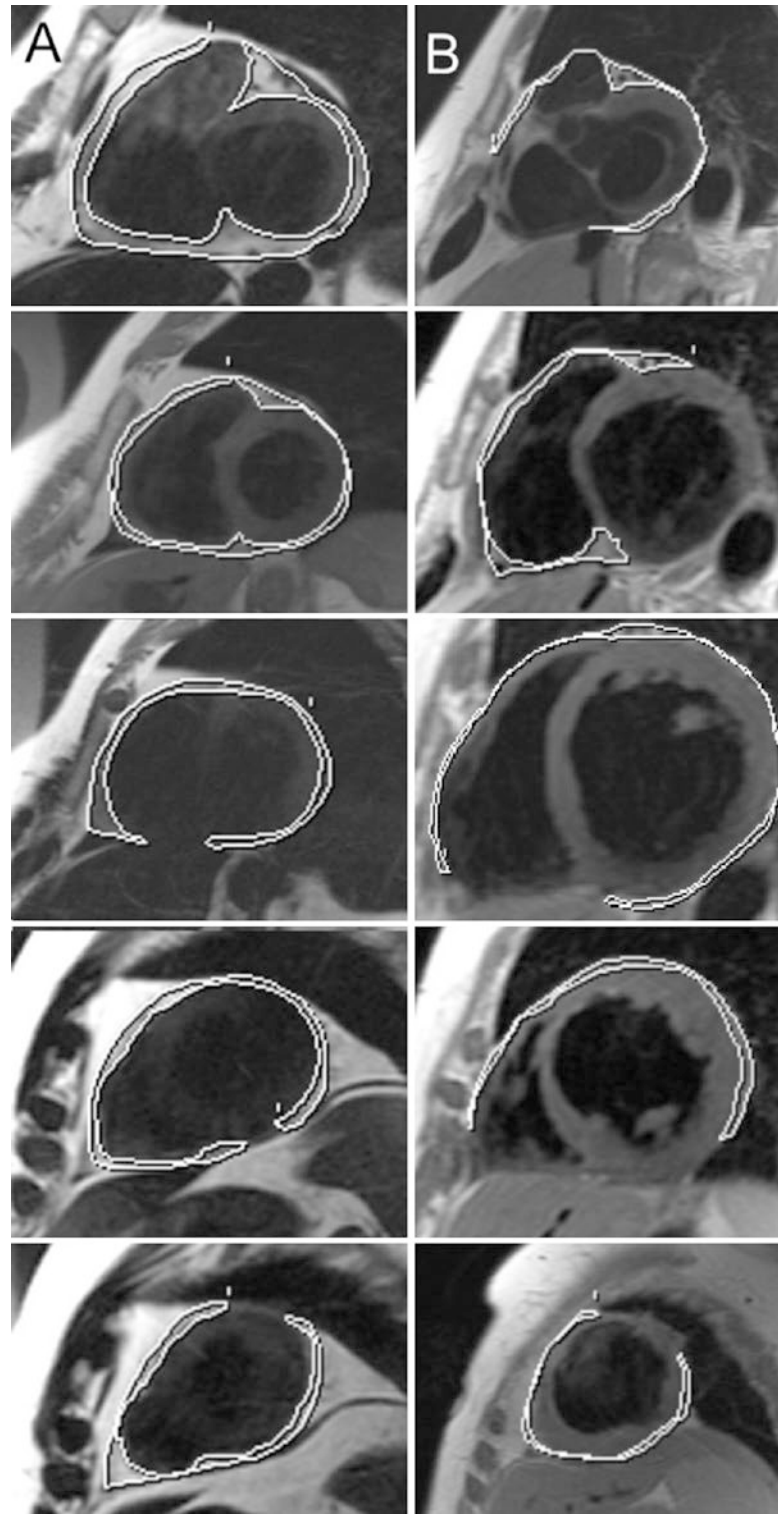

Fig. 11.1 EAT in healthy controls and patients with HFrEF. Volumetric measurement of EAT outlining the contours of EAT in end-diastolic images of short axis covering the left and right ventricles in a healthy control with normal EAT mass (*Panel A*) and in an HFrEF patient with reduced EAT mass (*Panel B*). CHF chronic heart failure, EAT Epicardial adipose tissue, and LV-EDM left ventricular end-diastolic mass. (From Doesch et al. [26], with permission)

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