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REVIEW ARTICLE

Epicardial adipose tissue: at the heart of the obesity complications

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Abstract In recent years, the anatomic and functional contiguity of epicardial adipose tissue (EAT) to myocardium and coronary arteries has gained increasing interest for its potential pathogenetic role in obesity-related cardiac diseases. Besides its known and attributed biochemical cardioprotective properties, it is becoming evident that, in metabolic disease states, EAT-secreted bioactive molecules may play an important role in the pathogenesis of coronary artery disease and cardiac arrhythmias. EAT-derived inflammatory cytokines and reactive oxidative species may, indeed, play a part in the development of a local proatherogenic milieu by paracrine and vasocrine mechanisms of interaction. In addition, initial clinical and in vitro studies have pointed out that EAT could be a determinant of the substrate of atrial fibrillation by contributing to the structural and electrical remodeling of myocardium. This article reviews the current state of knowledge on the association of EAT with cardiac dysfunction and the potential factors mediating the cross talk between this fat depot and the underlying cardiac structures.

Keywords Epicardial adipose tissue · Obesity · Coronary artery disease · Atrial fibrillation · Ectopic fat depots

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Introduction

In both developed and developing countries, the prevalence of obesity has reached an alarming level and has become a worldwide epidemic. This has stimulated an enormous research interest in the biology of adipose tissue and in its pathophysiological role in obesity-related complications and therefore gradually transformed adipose tissue from an inert lipid store into a metabolically dynamic endocrine organ capable of synthesizing biologically active compounds that regulate metabolic homeostasis, as well as a variety of biological functions [1–3].

It is well established that abdominal obesity confers increased risk of metabolic complications, whereas preferential fat accumulation in gluteofemoral region is associated with a lower risk [4] and, accordingly to lessons learned from lipodystrophies, may be even protective [5–7]. In addition, there are numerous smaller visceral adipose depots such as epicardial (EAT) and intermuscular adipose tissue [8] that may serve specialized functions related to their neighboring tissues [9]. However, unraveling the mechanisms that differentiate the clinical significance and specific contribution of each fat depot to cardiometabolic complications is challenging since location of different deposits, fundamental properties of adipocytes as well as systemic and local actions of adipokines and FFAs are involved [10, 11].

Fat depots around the heart

The nomenclature used to differentiate fat depots around the heart is often misleading, with several discrepancies and ambiguities among authors [12]. The term of 'paracardial fat' (also known as extrapericardial or intrathoracic)

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has been variably used to identify fat located on the outer surface of the fibrous pericardium [13]. EAT has been instead defined as the intrapericardial fat located between the myocardium and visceral pericardium, while the storage of triglycerides within the cardiomyocytes has been termed myocardial fat [12]. The term 'pericardial fat' is often used interchangeably with EAT, even though some groups used this term as a representative of the total fat around the heart, which is the sum of EAT and paracardial fat [14]. The thickness and volume of EAT and paracardial fat can be quantified by echocardiography and computed tomography or magnetic resonance imaging, respectively [8, 12, 15, 16].

EAT anatomy: what makes plausible the cross talk with myocardium and coronary vessels

The last decades have witnessed a growing interest in EAT, especially because EAT and myocardium share the same coronary blood supply and are not anatomically separated by any fascial plane, thereby making plausible a 'vasocrine' or 'paracrine' cross talk [9]. In contrast to pericardial fat which derives from the primitive thoracic mesenchyme, EAT originates from splanchnopleuric mesoderm as the omental fat [14].

EAT covers 80% of the heart's surface, representing 20% of the organ's total weight under normal conditions, although correlations with advancing age have also been reported [8, 17]. EAT is mainly found in the atrioventricular and interventricular grooves up to the apex, along the coronary arteries and around the atria.

As compared to other adipose depots, EAT is characterized by smaller adipocytes and greater adipocyte number per gram of tissue, and differences in protein and fatty acid composition have also been reported [18].

EAT physiology: between evidence and speculation

Unfortunately, since several findings have not been validated in animal models or in human EAT and species-specific differences in the physiological relevance of EAT should be expected, the insight into the biology of this unique fat depot remains limited, and further studies aiming at defining the cellular and molecular properties of EAT are still necessary.

However, due to its distinctive anatomic juxtaposition, numerous putative physiological roles have been attributed to EAT. Namely, EAT may attenuate vascular torsion, participate in vessel remodeling and cushion cardiac nervous ganglia; it may also exert metabolic functions representing an immediate energy source in high energy demand conditions and maintaining fatty acid homeostasis in the coronary microcirculation [19]. Indeed, epicardial adipocytes possess special properties to manage fatty acids, including high rates of fatty acid incorporation, synthesis and breakdown as well as insulin-induced lipogenesis [19]. EAT may also act as an immunological tissue protecting cardiac structures against pathogens and inflammatory activators [20] and reduce reactive oxygen species by lowering proton gradients formation [21]. Human EAT has been reported to exhibit high expression of uncoupling protein 1 (UCP1) [22] as well as of genes necessary for inducing browning of white adipose tissue and/or for classical brown adipose tissue development, such as CD137, PR domain containing 16 (PRDM16), peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1α), CCAAT/enhancer-binding protein α (C/EBPα), and peroxisome proliferator-activated receptor γ (PPARγ) [23]. But whether the presence of UCP1 protein turns into EAT having a higher thermogenic activity remains to be proved. Indeed, in humans undergoing 18fluorodeoxyglucose computed tomography-positron emission tomography fusion scans under experimental cold exposure conditions, the uptake of the tracer (that is the currently accepted criterion of active brown adipose tissue in vivo) is localized in the heart without a clear demarcation between the myocardial and EAT uptake [24]. Although it is becoming apparent that it is a relatively insensitive quantitative technique, the small amount of EAT compared to the much larger, thermogenic and active myocardium makes unlikely that EAT could have a direct thermoregulatory role during chronic cold challenge [23].

EAT may display cardioprotective properties by locally secreting anti-inflammatory and anti-atherogenic adipokines, which are adiponectin and adrenomedullin, whose protein levels correlate with their intracoronary levels [25, 26], and omentin that has been shown to ameliorate endothelial function by stimulating endothelial NO synthase and thus the production of nitric oxide [27].

EAT as marker of ectopic fat and metabolic derangements

EAT mass and thickness are increased in obesity [28], showing a stronger correlation with abdominal fat accumulation [29]. Increased EAT thickness or volume has also been shown to correlate with components of the metabolic syndrome, including fasting plasma glucose and insulin levels, insulin resistance (assessed by euglycemic hyperinsulinemic clamp or surrogate indices like HOMA and QUICKI), atherogenic lipid profile and systolic blood pressure [30, 31]. On the basis of echocardiographic measurements, definite cutoff values for EAT thickness

have been even proposed as metabolic syndrome predictors [32]. However, even though a recent meat-analysis supports the relationship between EAT and the metabolic syndrome independent of obesity, the multivariate analysis indicates that the relationship is not robust [33], suggesting that EAT should be mostly regarded as a marker of abdominal adiposity and ectopic fat and lipid storage. Indeed, with regard to the latter, EAT strongly and independently reflects the intramyocardial lipid content, as measured by proton magnetic resonance spectroscopy [34].

However, although the accretion of EAT appears of scarce systemic impact, its local pathophysiological significance has been rapidly growing supported by multiple lines of evidence from basic and translational science as well as from epidemiology.

The clinical relevance of EAT in coronary artery disease

Despite the above-mentioned associations between EAT amount and abdominal obesity, strong associations between EAT mass and coronary artery disease (CAD) have been found to be independent of measures of body fatness, including intra-abdominal fat [18]. Indeed, EAT volume was independently associated with cardiovascular disease, even after adjusting for body mass index (BMI) and waist circumference [35]. Recently, EAT volume resulted positively and independently associated with coronary artery calcium scoring [36], and able to predict coronary reserve in normal arteries [18]. Besides, non-obese subjects affected by CAD were shown to have higher EAT volume compared to those without CAD [37].

When EAT volume was measured in subjects stratified according to the presence of CAD and obesity, the differences in EAT volume in relation to the presence of CAD were exclusively observed in non-obese patients [37]. In line with other observations [16, 36], this suggests that the contribution of EAT to the coronary atherosclerotic burden is more relevant in non-obese than in obese patients and raises the issue of whether obesity may conceal the pathogenetic effects of EAT on CAD progression. Alternatively, it can be theorized that the factors mediating the association between EAT and CAD might change when obesity develops [38].

Instead, whether EAT volume is an indicator for the severity of CAD is still controversial [18].

The direct involvement of EAT in CAD pathogenesis is also sustained by the evidence that intramyocardial segments of coronary arteries, which are, therefore, not in contact with EAT, are not affected by atherosclerosis [39] and that the selective surgical excision of the portion of EAT covering the coronary artery of a pig model of CAD attenuated the underlying plaque progression in vivo [40].

The association between EAT and CAD from a pathophysiologic perspective

This epidemiological and experimental evidence together with histopathological data showing the presence of dense inflammatory infiltrates, mainly represented by macrophages, lymphocytes and mast cells, in EAT of CAD patients [41, 42], is the basis for the hypothesis that EAT might locally and detrimentally contribute to coronary atherogenesis.

Innate immunity can be activated within EAT by Toll-like receptors (TLRs) binding, with consequent nuclear factor-kappaB (NFkappaB) translocation into the nucleus inflammatory mediators transcription [42]. As such, EAT sampled from subjects with CAD showed higher NFkappaB, c-Jun N-terminal kinase (JNK) activity, TLR-2 and TLR-4 expression levels, all indicative of macrophage recruitment and activation [42]. Of interest, a recent study using next-generation sequencing technologies demonstrated the presence of bacterial DNA into EAT surrounding diseased coronary arteries, suggesting that EAT is susceptible to microbial colonization that might, thereby, contribute to elicit a proinflammatory response [43].

In CAD patients, EAT expresses and secretes higher levels of proinflammatory markers as compared to subcutaneous fat, such as IL-1β, IL-6, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), regulated upon activation T cell and secreted (RANTES) and soluble intercellular adhesion molecules (ICAMs) [18, 41], which have been proven to take part in various steps of the atherosclerotic process, from endothelial dysfunction to plaque instability and rupture. In the presence of CAD, elevated expression of IL-6, leptin, resistin, TNF-α and visfatin has been also described [18]. In addition, the mRNA levels of secretory type II phospholipase A2 (sPLA2-IIA), an enzyme promoting the generation of more atherogenic low-density lipoproteins and phospholipid products in the artery wall and their retention of in the subendothelial space, have been found increased in EAT from CAD patients [18]. In CAD conditions, as shown by proteomic and secretome analyses, EAT-derived mediators are capable of inducing cell surface expression of adhesion molecules in monocytes and endothelial cells [44], and FFAs released by EAT in the proximity of coronary arteries can modulate vascular responsiveness to vasoactive agents [45]. Contrariwise, EAT anti-inflammatory and anti-atherogenic adipokines (adiponectin and adrenomedullin) are down-regulated in chronic CAD, and increase in intracoronary adrenomedullin levels has been reported only

when hemodynamic conditions improve as after coronary revascularization [25, 26] (Fig. 1).

Furthermore, the expression levels of glucose transporter-4 (GLUT4) are lower, whereas those of renitol-binding protein 4 (RBP4) are higher in EAT from CAD compared to non-CAD subjects [46], suggesting that EAT may partly be responsible for local insulin resistance and altered glucose and lipid profile, which, in turn, can promote atherogenic changes in coronary vessels.

Finally, a higher oxidative stress, which also actively participates in the development and progression of atherosclerotic plaques, has been reported in EAT from CAD patients, as shown by higher levels of reactive oxygen species and lower levels of catalase (an antioxidant enzyme) compared to subcutaneous fat [46]. Recent studies have also reported that the increased oxidative stress characterizing EAT of CAD patients is capable of promoting transdifferentiation of brown to white adipocytes [47] and that an increase in 'brown' features of EAT could predict the stability of coronary atheromas in humans [48]. These data support the hypothesis that the presence of adipocytes with brown features in EAT might also contribute to render the local environment proatherogenic.

The juxtaposition of EAT to myocardium and coronary arteries makes plausible vasocrine (via vasa vasorum) or paracrine (via interstitial fluids) signaling between adipokines and FFAs diffusing from EAT [9, 49]. Besides, cells migrating between these adjacent structures may also contribute to spread inflammation to the surrounding tissues [12].

Although it is so far unclear whether EAT inflammation derives from the underlying plaque inflammation or EAT is intrinsically and primarily inflamed, a bidirectional flow of inflammatory mediators cannot be excluded.

The emerging role of EAT in cardiac arrhythmias

In obese patients, EAT amount was found to be associated with alterations in cardiac morphology and function such as increased left ventricular mass, right ventricular cavity size, atrial enlargement and diastolic dysfunction [49].

Although these alterations may be due to obesity-induced hemodynamic changes, low-grade inflammation state and oxidative stress [50, 51], there is growing evidence of a potential direct role of EAT in their development.

Indeed, several recent studies have established the association of EAT with atrial fibrillation onset, chronicity, recurrence after catheter ablation or electrical cardioversion and symptom burden, as independent of other atrial fibrillation risk factors (i.e., left atrium size) and systemic adiposity [50, 52, 53]. The abundance of EAT independently predicts lone atrial fibrillation, but also of atrial fibrillation associated with hypertrophic cardiomyopathy or CAD and after coronary bypass [51, 54, 55].

The comparison of the extension and localization of high-dominant frequency and complex fractionated atrial electrograms suggests that EAT might contribute to the formation of the substrate of atrial fibrillation, possibly promoting atrial structural and electrical remodeling [50]. In fact, in line with other fat depots [56, 57], not only extracellular matrix proteins are remarkably increased in EAT in cardiac pathological conditions [58], but EAT may also induce fibrosis in the neighboring myocardium through the secretion of profibrotic mediators including inflammatory cytokines, growth factors and matrix metalloproteinases [59, 60] (Fig. 1). When the secretome of EAT, but not of parasternal subcutaneous fat, obtained from CAD patients was applied on atrial myocardium in an ex vivo model, it induced a transformation of fibroblasts into myofibroblasts and subsequent massive myocardial fibrosis.

Among the EAT-secreted factors, activin A resulted one of the main potential mediators of the profibrotic effect of EAT secretome on atrial myocardium [59]. Of note, activin A concentration in the EAT secretome is highly variable, with higher levels in predisposing conditions for atrial arrhythmias, such as heart failure [59], obesity and type 2 diabetes [60]. Of note, type 2 diabetes-induced alterations in the secretory profile of EAT have been even overall associated with the development of insulin resistance and negative inotropic effects in rat cardiomyocytes, suggesting that in type 2 diabetes EAT could also locally contribute to the pathogenesis of cardiomyopathy [60].

However, both the abundance of EAT at sites which are common targets for atrial fibrillation catheter ablation (i.e., at the antra of pulmonary veins) and the dense autonomic innervation of EAT may suggest that EAT could act as a trigger and a modulator of the sympathetic and parasympathetic tone in arrhythmias [50]. After all, EAT is a source of inflammatory cytokines and reactive oxygen species, known to be associated with a high incidence of atrial fibrillation, as well as of adipokines involved in calcium homeostasis of cardiomyocytes and, therefore, in the electrical properties of the atria [60].

Finally, the presence of marked myocardial fibro-fatty infiltration in cardiac disorders strictly associated with the development of ventricular arrhythmias, such as the arrhythmogenic right ventricular cardiomyopathy and the myotonic dystrophy, as well as in an ovine model of ischemic cardiomyopathy [61], suggests that EAT may also play a role in the pathogenesis of ventricular arrhythmias.

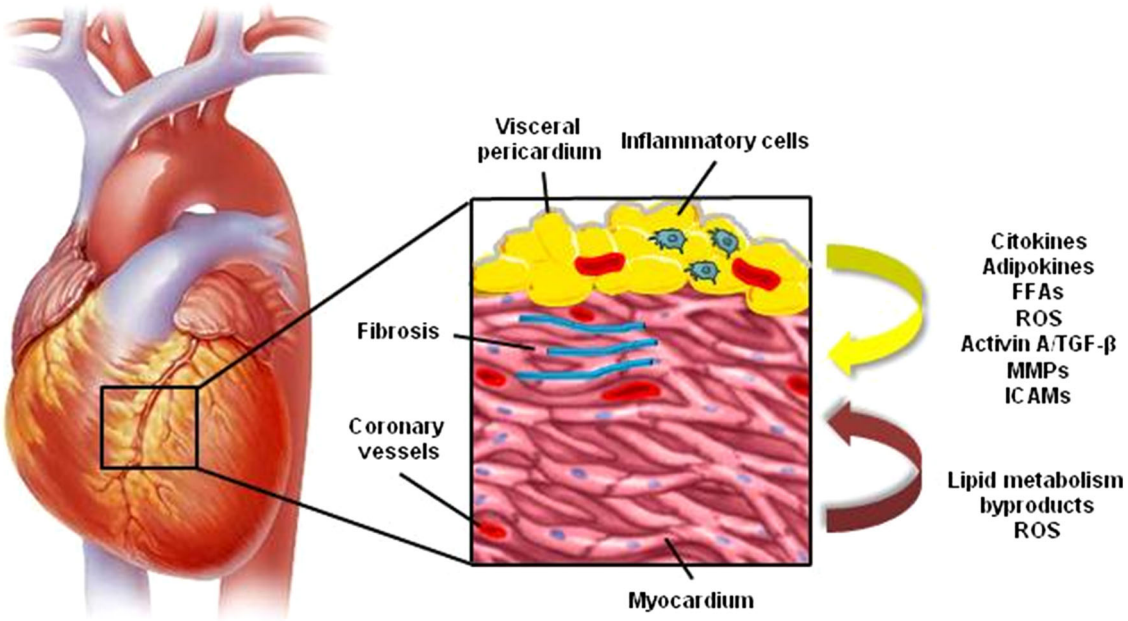

Fig. 1 Potential signaling pathways mediating the cross talk between EAT, myocardium and coronary vessels

Does EAT location matter?

Necropsic and multidetector computed tomography studies have shown that EAT is not homogeneously distributed and reported regional variation in the strengths of associations between different measurements of EAT and anthropometric indexes [16]. Similarly, EAT thickness measured at the level of the left atrioventricular groove, but not over the right ventricular free wall, was related to clustering of metabolic syndrome components and inflammatory markers [16], whereas the peri-atrial EAT volume resulted the most strictly associated with the incidence atrial fibrillation [62].

At molecular level, Spiroglou et al. [63] reported different patterns of adipokine expression (adiponectin, visfatin, leptin, chemerin, and vaspin) between peri-coronary and apical EAT, failing to find any correlation between coronary atherosclerosis and adipokine expression in EAT of the apical region.

A recent study, by using a pangenomic approach, even defined specific transcriptomic signatures of EAT at different anatomical locations as suggestive of different EAT properties with respect to the adjacent structures. In particular, the peri-coronary EAT resulted more closely involved in atherotic plaques formation, expressing genes involved in cell proliferation and in metabolism of sphingolipids which are lipid components of atheromas capable of promoting oxidized LDL and VLDL retention in the sub-endothelial space. In contrast, peri-ventricular EAT was more strictly linked to genes regulating inflammatory pathways, whereas the genes most up-regulated by peri-atrial EAT were implicated in energy metabolism, cardiomyocyte contractility and intracellular calcium signaling [64].

Therapeutic interventions

Changes in nutritional [65, 66] or physical activity [67, 68], and more recently bariatric surgery [69–71], are the mainstay interventions for obese and type 2 diabetic patients. In this context, EAT has been discussed as a target for the treatment and prevention of obesity cardiovascular complications.

Weight loss following dietary as well as bariatric surgery interventions was significantly associated with reductions in EAT, whereas the impact of physical exercise on EAT amount is less established [72]. The effect on EAT by medications has been also evaluated. Park et al. [73] reported a significant decrease in EAT thickness in patients treated with atorvastatin, whereas it increased during pioglitazone treatment [74].

However, the amount of EAT reduction cannot be predicted by the overall amount of weight loss, as most impressively demonstrated by the finding that, in spite of the much greater reduction in body weight occurred by means of bariatric surgery, EAT decrease was similar to that observed in the group of patients undergone dietary intervention [72]. This could suggest that there is a limit on the possible EAT reduction in humans consistently with the

need for EAT to retain its physiologic role, but also that EAT responses to weight loss strategies may vary from those of larger visceral fat depots.

All together, these observations highlight that additional epidemiological and experimental research is needed not only to provide evidence of a definite causal relationship between EAT and obesity-related cardiac dysfunctions and to unravel mechanistically their link, but also to investigate the beneficial effect of therapeutic interventions aiming at EAT reduction.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

Informed consent For this type of study formal consent is not required.

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