International Journal of Cardiology 278 (2019) 254–260

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Epicardial adipose tissue and cardiovascular diseases

Anna Maria Ansaldo [a], Fabrizio Montecucco [b,c], Amirhossein Sahebkar [d,e,f], Franco Dallegri [b,c], Federico Carbone [a,*]

[a] Department of Internal Medicine, University of Genoa, 6 viale Benedetto XV, 16132 Genoa, Italy
[b] First Clinic of Internal Medicine, Department of Internal Medicine, and Centre of Excellence for Biomedical Research (CEBR), University of Genoa, 6 viale Benedetto XV, 16132 Genoa, Italy
[c] IRCCS Ospedale Policlinico San Martino Genoa - Italian Cardiovascular Network, 10 Largo Benzi, 16132 Genoa, Italy
[d] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran
[e] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[f] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article history:
Received 7 June 2018
Received in revised form 20 September 2018
Accepted 24 September 2018
Available online 1 October 2018

Keywords:
Epicardial adipose tissue
Atherosclerosis
Heart failure
Atrial fibrillation
Inflammation
Cardiovascular

ABSTRACT

Obesity is a heterogeneous disease with different degrees of cardiovascular (CV) and metabolic manifestations. Certain ectopic fat depots may contribute to obesity-related CV risk and may explain part of the risk differential observed in metabolically healthy obese and the so called "obesity paradox". The growing interest towards the potential impact of epicardial adipose tissue (EAT) in cardiovascular (CV) risk has led to deepen its biological function. Genetic, epigenetic and environmental factors may drive the shift towards a dysfunctional EAT characterized by a pro-inflammatory and pro-fibrotic phenotype. Due to the close anatomic proximity to coronary arteries, a thicker and dysfunctional EAT actively contribute to development and progression of coronary atherosclerosis. Beside classical paracrine transmission, EAT may directly release mediators into the vasa vasorum of the coronary arterial wall, a mechanism referred to as "vasocrine". Similarly, the pro-inflammatory and pro-fibrotic secretome characterizing dysfunctional EAT may impair cardiac structure and function, thus being implicated in the pathogenesis of diastolic heart failure and atrial fibrillation. The development of 3D imaging techniques have paved the way for clarifying the causative role of EAT in CV pathophysiology, the use of EAT volume/thickness in CV risk stratification and potential cardio-protective effects of EAT reduction. The aim of this narrative review is to update current knowledge on the pathophysiological functions of EAT, focusing on basic mechanisms and potential clinical implications.

1. Introduction

Since decades, the body mass index (BMI) and fat mass have been recognized as leading determinants of metabolic health. However, obesity is a remarkably heterogeneous condition with different degrees of cardiovascular (CV) and metabolic manifestations [1–4]. Several studies have clearly established a close relationship between visceral and ectopic fat and the development of metabolic derangements. Ectopic fat depots may contribute to obesity-related CV risk and may explain part of this "differential" risk. This relationship becomes even more important when clinical entities, such as "metabolically healthy" obesity phenotypes and the "obesity paradox", are considered. Ectopic fat is defined by excess of adipose tissue located outside of classical adipose tissue deposits. The pathophysiological mechanisms underlying the shift from subcutaneous to ectopic fat deposition have not been elucidated yet. Those factors were likely described as multifactorial, involving genetic, epigenetic and environmental factors [5]. Ectopic fat depots may be categorized based on their location as well as association with either systemic or local effects. Predominantly systemic effects have been reported for visceral adipose tissue, intrahepatic and intramuscular fat. Prevalent local activity was instead recognized in the kidney and heart. The latter should be further classified in paracardial and epicardial adipose tissue (EAT), which in turn includes fat depots located between the myocardium and the visceral pericardium (i.e. pericardial fat, perivascular fat, and myocardial steatosis). The growing interest towards the potential impact of EAT in CV risk has led to deepen its biological function. Therefore, we will focus on updating the current knowledge about the metabolic changes occurring in dysfunctional EAT, the interaction with surrounding tissues (i.e. coronary vessel wall and cardiomyocytes) and the clinical implications on atherosclerosis and myocardial diseases. Finally, we will discuss on future perspectives in terms of imaging methods for EAT quantification and cardio-protective effects of EAT reduction.

* Corresponding author.
E-mail address: federico.carbone@edu.unige.it (F. Carbone).

https://doi.org/10.1016/j.ijcard.2018.09.089
0167-5273/

2. Epicardial adipose tissue: normal morphology and physiology

EAT exhibits embryological and morphological similarities with visceral fat, both originating from splanchnopleuric mesoderm. EAT is located between the myocardium and visceral pericardium, mainly on the right ventricle surface and anterior wall of the left ventricle. EAT also surrounds atrioventricular grooves and great coronary vessels, reaching the main thickness at the anterior and lateral walls of right atrium. Due to the elasticity and compressibility EAT exerts a mechanical function, protecting coronary arteries against the excessive warp caused by artery pulse and myocardial contraction [6]. Interestingly, EAT and myocardium are not separated by connective or aponeurotic tissues, suggesting a close and strong interaction between these two structures. Under physiological conditions, EAT covers nearly the 80% of the heart surface and contributes for the 20% to the whole heart mass. EAT volume and thickness is likely to be determined by genetic, epigenetic, and environmental factors. In this regard, larger EAT mass has been found in non-Hispanic White or Japanese than in African Americans, whereas a two-fold increase was observed in patients with body mass index (BMI) higher than 27 kg/m^2. Other environmental factors such as aging, excess caloric intake, sedentary life style, pollutants, and microbiota may also modulate ectopic fat deposition [7]. Histological analysis of EAT reveals a mixed cellularity characterized by abundant and smaller adipocytes stromal cells and a large amount of resident inflammatory cells, such as lymphocytes (CD3$^+$ cells), macrophages (CD68$^+$ cells), and mast cells. Noteworthy, EAT is also characterized by nervous and nodal tissue with high production of nerve growth factor, thus suggesting a potential role of EAT as a scaffold for cardiac autonomic nerves and ganglionated plexi. Differently from the pericardial fat, EAT vascularization is dependent on the branches of coronary arteries, further indicating a close relationship between EAT and underlying myocardial tissue [6]. As widely recognized, adipose tissue is not only simple lipid storage units. Rather, it also serves as a paracrine/endocrine organ, with a key role in lipid and glucose homeostasis. In particular, EAT serves as a local store for the excess of FFAs, thus maintaining myocardial energy supply and preventing the toxic effects of high circulating FFAs on myocardium and coronary arteries. Conversely, under metabolic stress conditions, EAT may releases free fatty acids (FFAs) with a rate higher than other adipose tissue depots. EAT handles FFAs homeostasis through the coronary circulation, the bidirectional flux through the interstitial fluid and the expression of fatty acid transporters (e.g. fatty acid binding protein-4 [FABP-4]) [8]. The homeostatic function of EAT also includes the control of vascular tension. EAT controls the effect of insulin on microcirculatory networks, thus promoting insulin-mediated vasoreactivity and glucose uptake in the coronary vascular bed [9]. Through the release of adipocytokines (mainly adiponectin, adrenomedullin and omentin) and adipocyte-derived relaxing factors, EAT further lowers vascular tension and prevents vascular remodeling [10]. The binding of adiponectin to the Adipo1 and Adipo2 receptors, activates a signaling cascade that promotes synthesis and release of nitric oxide and blunts the NF-κB-mediated pro-inflammatory signaling. In normal conditions, EAT also release a large amount of adrenomedullin a potential vasodilator peptide. Adrenomedullin antagonizes oxidative stress induced by angiotensin II, inhibits migration and proliferation of vascular smooth muscle cells (VSMCs), and suppress endothelial cell apoptosis and endothelin-1 release [11]. Finally, adrenomedullin contributes to cardiac output by increasing intracellular calcium concentration in cardiomyocytes.

3. The phenotypic shift towards dysfunctional epicardial adipose tissue

EAT was suggested to be more than a simple adipose tissue depot, since it is an extraordinarily active endocrine organ and its wide secretome may have either a safety or detrimental effect depending on the local microenvironment (Fig. 1) [12]. Similarly to the visceral adipose tissue (VAT), pathological stressful conditions, such as obesity, insulin resistance, diabetes and vascular damage may promote the shift of EAT towards a pro-inflammatory and pro-fibrotic phenotype. In these conditions an impressive changes in EAT secretome occurs, finally leading to hypertrophy, failure of triglyceride storing, increased lipolysis and inflammation. In patients with metabolic syndrome (MetS) the thickness of EAT reaches 7.5 mm as compared to 4 mm in control patients. Given its close anatomic proximity to the coronary arteries, a thicker and dysfunctional EAT is directly involved in the development and progression of coronary and myocardial diseases. The expansion of adipocytes within EAT is accompanied by the up-regulation of pro-inflammatory factors and infiltrations of immune cells (i.e. dendritic cells, T and B cells, macrophages and eosinophils). More specifically, the up-regulation nuclear factor κB (NF-κB) and c-Jun N-terminal kinase (JNK) activities determines higher mRNA expression of inflammatory mediators (e.g. IL-1β, IL-6, TNFα, MCP-1), toll-like receptor (TLR)-2 and -4, sPLA2-IIA, resistin and visfatin. Furthermore, whereas CD206$^+$ cells, corresponding to the anti-inflammatory macrophages (M2), are commonly found in EAT, a shift towards the pro-inflammatory phenotype (M1), characterized by positivity for CD11c, is observed in the dysfunctional EAT [13]. Such M1 polarization is closely related to the loss of angiotensin (Ang)-converting enzyme (ACE)2 [14]. As observed in knockout mice, the loss of ACE2 results in impaired glucose tolerance, epicardial EAT inflammation, and M1 macrophage polarization. Conversely, the administration of Ang 1-7, an ACE2-mediated degradation product of Ang II, reduced EAT inflammation and reverses macrophage polarization [15]. Pro-inflammatory M1 macrophages are also associated with EAT neoangiogenesis, interfering with both adiponectin and FABP-4 production. All those features may alter homeostasis of the surrounding epicardial arteries, thus potentially amplifying vascular inflammation and plaque instability [8,16,17]. Conversely, treatments with simvastatin and pioglitazone have been shown to induce anti-inflammatory effects [18]. Even though, whether EAT inflammation is the cause or reaction to coronary plaques still remains unknown [19]. Very recently, also microbial colonization of EAT has been indicated as an additional pathway for a dysfunctional adipose depot. Indeed, a broad range of bacterial species was associated with NALP3/inflammasome pathway activation within EAT in patients with acute coronary syndrome (ACS).

4. The "vasocrine" cross-talk between EAT and surrounding coronary arteries

Due to the close proximity to the myocardium, EAT acts as metabolic transducer for different mediators that easily diffuse from EAT to vessel wall [20]. Through the paracrine transmission, cytokines from EAT diffuse across the interstitial fluid into the arterial layers wall and finally interact with endothelial and VSMCs. As alternative mechanism, cytokines and FFAs from EAT may be directly released into the vasa vasorum of the coronary arterial wall. As these vessels are unlikely to access the systemic circulation, thus limiting their activity to the arteriolar and capillary endothelium, this mechanism is termed as "vasocrine". This latter is considered the prevalent mechanism in case of advanced atherosclerotic lesions, where paracrine diffusion becomes difficult. Most recent studies have highlighted the role of microparticle-mediated genetic exchange in the crosstalk between EAT and coronary arterial wall. Especially exosomes, nano-sized (30–100 nm) extracellular vesicles, are able to carry a wide range of otherwise degradable molecules to recipient cells (proteins, lipids, ribonucleic acids [RNAs]). The exosomal cargo is extremely variable and largely dependent of cell types and microenvironment. Among them, exosomes would facilitate transportation and delivery of EAT-derived microRNAs (miRNAs) to the target cells. MiRNAs are a class of short non-coding RNAs (21–25 nucleotides in length) that regulate post-transcriptional synthesis of proteins by interfering with mRNA transcription and translation. Generally associated with reduced yield of protein, miRNA may also have the

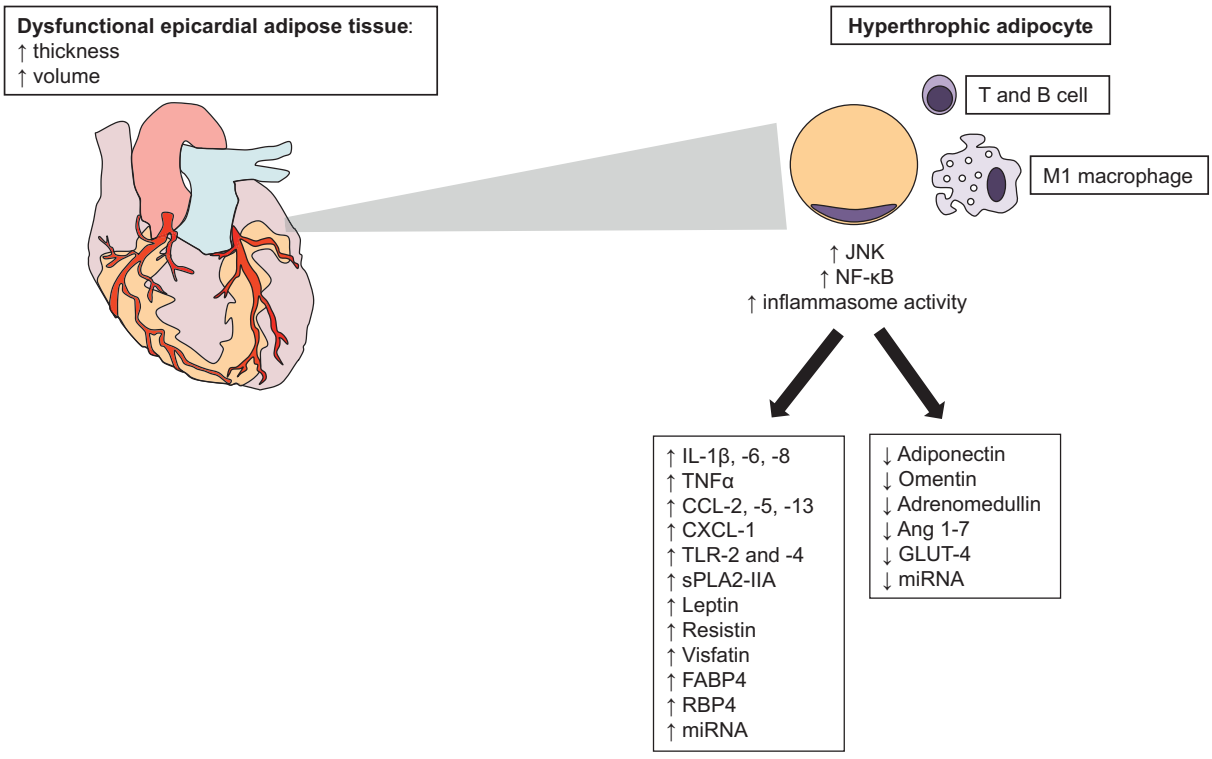

Fig. 1. Secretome changes in dysfunctional epicardial adipose tissue. Dysfunctional adipose tissue is characterized by adipocyte hypertrophy and infiltration of immune cells (i.e. T and B lymphocytes and pro-inflammatory [M1] macrophages) Those histopathological features determine impressive changes in adipocyte secretome, which is characterized by increase of pro-inflammatory and pro-fibrotic mediators (interleukins [ILs], C-C and CXC motif chemokine ligand [CCL, CXCL], toll like receptors [TLRs], secretory phospholipase A2 type IIA [sPLA2-IIA], fatty acid binding protein [FABP], retinol binding protein [RBP] and microRNA [miRNA]) and suppression of anti-inflammatory mediators (e.g. angiotensin [Ang] 1-7 and glucose transporter [GLUT]).

opposite effect to enhance protein transcription. The development of next generation sequencing allowed to identify EAT as a leading source of circulating miRNA. In adipocytes, miRNAs were shown to act on multiple targets with effect on adipocyte differentiation and metabolic homeostasis. During metabolic diseases, miRNAs (i.e. miR-103-3b and miR-143) are differentially modulated in adipose tissue showing suppression of lipid- and retinoid-sensing nuclear receptors, activation of innate and adaptive immune responses (e.g. up-regulation of MHC Class II) and enhanced communication with inflammatory cells (e.g. up-regulation of CCL5, CCL13, and CCL5R expression). The extent of interaction between EAT-derived microparticles and surrounding cells is still unclear, but experimental studies hypothesized that these particles are able to promote monocyte migration and pro-inflammatory polarization [21]. Noteworthy, a backward cross talk to EAT has been recently recognized. Indeed, intravenous infusion of endothelial cell-derived microparticles containing miR-19b was shown to accelerated atherosclerosis and promote EAT inflammation in apoE$^{-/-}$ mice [22].

5. Epicardial adipose tissue and coronary atherosclerosis

Although the exact mechanisms are not yet fully elucidated, a growing body of evidence supports the role of EAT as a promoter of atherosclerotic plaque progression and vulnerability [12]. Integrative miRNA and whole genome analyses identified the signature of miRNAs in EAT of CAD patients, by focusing on miR-103-3p downregulation as prominent features. This pattern affected metabolic pathways with suppression of lipid and retinoid-sensing nuclear receptors, transcriptional activities, in addition to sustain a pro-inflammatory environment, characterized by suppression of adiponectin release and high levels of IL-1, IL-6, IL-8, CCL-2, CCL-5, CCL-13, TNFα, and GRO-α. Even in the early stage of atherogenesis, the altered secretome stimulates monocyte adhesion by up-regulating ICAM-1 expression of endothelial cell surface. The typical secretome of dysfunctional EAT is also associated with VSMC migration and activation, but this effect is blunted by omentin [23]. In line with experimental evidence, clinical studies support the close association of dysfunctional EAT with coronary artery disease (CAD) degree and severity. Two meta-analyses published in 2017 confirmed this association independently of CAD definition: obstructive or significant coronary stenosis, coronary artery calcification (CAC) or myocardial ischemia [24,25]. Furthermore, clinical data emphasized the relationship between EAT and different features of plaque vulnerability, such as thin-cap of the fibroatheromas, high percentage of necrosis, elevated endoluminal stenosis and presence of calcification [26–31]. It is then not surprising that several studies report a predictive role of dysfunctional EAT towards the occurrence of major adverse cardiovascular events (i.e. CV death, myocardial infarction [MI], unstable angina, intra-stent re-stenosis) [32–39] (Table 1). Furthermore, EAT has been associated with culprit lesions and infarct-related artery patency, being a predictor of lower TIMI flow in patients with ST-elevation MI [40,41]. Noteworthy, the distribution rather than total volume seems to be the better predictor, thus supporting a prevalent paracrine activity of EAT [42]. Especially peri-coronary adipose tissue seems to be more implicated in atherogenesis, likely due to the expression of genes involved in cell proliferation and sphingolipids metabolism [43,44]. Finally, EAT has been suggested to influence myocardial healing by regulating granulopoiesis, fibrosis, and ultimately cardiac function after MI [45–48].

6. Association between dysfunctional EAT and metabolic dysfunction

Echocardiographic-assessed EAT is primarily considered a marker of visceral adiposity. Indeed, EAT thickness is closely related to abdominal fat, being usually increased in obese subjects. As expected, EAT thickness also correlates with MetS and relative clinical features such as high blood pressure, high levels of low-density lipoprotein cholesterol and insulin resistance [49]. However, the strength of the association with metabolic component is less than one-half of that with obesity

Table 1
Studies reporting an association between epicardial adipose tissue (EAT) and the risk of adverse coronary events.

Author	Year	Study design	EAT measure (follow-up)	Outcome
Mahabadi et al. [32]	2013	Prospective observational 4093 patients free of CVD	EAT volume (8.0 ± 1.5 years)	Incidence of coronary events ($n = 130$) increased by quartile of EAT ($p < 0.001$ for trend). EAT doubling of EAT was associated with a 1.5-fold risk of coronary events also after when adjustment for CV risk factors (95% CI 1.07 to 2.11).
Kunita et al. [33]	2014	Cross-sectional 722 CAD patients underwent CT	EAT volume (3.7 ± 1.7 years)	Event rates ($n = 37$) increased across CAC score categories (p for trend <0.001). They were significantly higher in the higher EAT volume group (adjusted HR 2.65 [95% CI 1.23–5.70]; $p = 0.009$).
Gitsioudis et al. [34]	2016	Prospective observational 177 asymptomatic individuals	EAT volume (3.2 ± 1.1 years)	Event rates ($n = 10$) increased across EAT volumes (adjusted HR 4.08 [95% CI 1.28–12.97]; $p = 0.009$).
Homsi et al. [35]	2016	Case-control 22 MI and 33 non-MI hypertensive patients	EAT volume	Higher EAT volume was found in MI patients, independently of age, BMI or heart rate ($p < 0.05$)
Mahabadi et al. [36]	2016	Prospective observational 241/3630 subjects developing MACE	EAT volume	EAT volume predicts MACE (HR: 1.15 [95% CI: 1.01–1.30]) improving the predictive value of the combined Framingham Risk Score/CAC evaluation (AUC = 0.749 to 0.764; $p = 0.011$).
Mahabadi et al. [37]	2017	Retrospective observational 94 patients with confirmed or suspected CAD	EAT volume	EAT volume was independently associated with the occurrence of type-I myocardial infarction (OR 1.79 [95% CI 1.10–2.94]; $p = 0.02$).
Goeller et al. [38]	2018	Prospective observational 456 asymptomatic individuals	EAT density 13.2 years ± 2.1 years (13.2 ± 2.1 years)	EAT density was more significantly associated with MACE (HR 0.8 [95% 0.7–0.98]; $p = 0.029$) than EAT volume or CCS.
Morales-Portano et al. [39]	2018	Prospective observational 107 subjects undergoing coronary angiography	Mean EAT thickness (15.94 ± 3.6 months)	At interquartile analysis EAT provided a better discrimination range for MACEs, and higher, more significant adjusted risk (cutoff 4.6 mm, RR3.91 [95% CI 1.01–15.08]; $p = 0.04$) than the other risk factors.

CVD: cardiovascular disease; CV: cardiovascular; CI: confidence interval; CAD: coronary artery disease; CAC: coronary artery calcification; HR: hazard ratio; MI: myocardial infarction: BMI: body mass index; MACE: major adverse cardiovascular events; AUC: area under the curve; CCS: coronary calcium score; RR: relative risk.

indices, especially visceral adipose tissue [50]. Considering that and the wide variability due to gender and ethnicity, there are not specific cut-off points of EAT thickness associated with prevalence or risk of MetS [51]. Nevertheless, a single-slice EAT area measurement at left main coronary artery (LMCA) was shown to increased linearly with increasing number of MetS components, thus representing a simple and reliable tool for diagnosis of MetS [52]. Especially, the relation between EAT and T2DM has been recently evaluated. Ticker EAT characterizes diabetic patients [53] and positive associations with BMI, visceral adiposity, and waist circumference have been reported [54]. Cytokines released from dysfunctional endothelium may directly contribute to reduce insulin signaling by reversing the glucose transporter-4 (GLUT4) to retinol binding protein 4 (RBP4) ratio [55]. The suppression of glucose uptake and lipogenesis combined with the increased release of FFA has been then reported in CAD and heart failure (HF), independently of diabetes [56]. Similarly, in non-diabetic patients a strong positive correlation between fasting plasma glucose and dysfunctional EAT was reported [57]. EAT volume and thickness may be then considered as surrogate markers of insulin resistance and different cut-off values have been proposed. Of interest, EAT has been also evaluated in the setting of type 1 diabetes (T1DM). In those patients EAT is thicker and inversely associated with endothelial function, independently of age, BMI or levels of glycated hemoglobin [58]. However, a causal effect of EAT in T1DM-related injury is not yet established, also considering the strong association with BMI, waist-to-hip ratio, glycated hemoglobin, triglyceride level and history of degree of renal disease [59].

7. Epicardial adipose tissue and heart failure

EAT thickness is directly associated with left ventricular mass (LVM), independently of BMI [60]. Especially EAT accumulation around the right ventricle is associated with enlarged right ventricular mass in obese subjects, whereas other studies also focused of the relationship between EAT and cardiac function. Epicardial fat amount correlates with myocardial fibrosis, and impaired LV diastolic function, independently of metabolic status or the presence of CAD. However, controversial data exist, partially due to the lowering of adipose mass in individuals with HF [61,62] (Table 2) [45,63–70]. It has been supposed that ETA is involved in the fibrotic transformation occurring in chronic HF and a recent focus has shifted from the 'quantity' to the 'quality' of EAT [72]. Pro-inflammatory polarization of EAT is common in HF patients and the consequent changes in EAT secretome have modulating properties on cardiac function [14,73]. Cardio-suppressive effects of adipocytokines (e.g. IL-1β, IL-6, TNFα, C1q/TNF-Related Protein-1, MCP-1, RPB4) include reduction in sarcomere shortening, cytosolic Ca^{++} fluxes, expression of sarcoplasmic endoplasmic reticulum ATPase 2a, activation of AMPK signaling pathway, and decreased insulin-mediated Akt-Ser473-phosphorylation [74]. Furthermore, ACE2/Ang 1-7 axis is increasingly emerging as critical regulator of EAT-induced cardiac dysfunction. Local activation of renin-angiotensin system may affect cardiomyocyte energy metabolism through the expression of miR-208a, leading to cardiac steatosis, lipotoxicity, and impaired mitochondrial respiration and insulin resistance. Those findings actively contribute to worsen heart function as observed in both human cohorts and experimental models (i.e. $ACE2^{-/-}$ mice) [14]. Further confirming this hypothesis, the leptin-aldosterone-neprilysin axis has been recently indicated as an additional pathway linking EAT dysfunction to the development of HF, alongside with the suppression of thermogenic genes (e.g. uncoupling protein 1, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, and PR-domain-missing 16) [75].

8. Epicardial adipose tissue and atrial fibrillation

Whereas several studies largely demonstrated obesity as an independent risk factor for atrial fibrillation (AF) [76], only in recent studies the excess of EAT has been implicated in AF onset, severity and recurrence. Moreover, this association seems to be independent of total adiposity or left atrial enlargement [77]. It has been then supposed that especially posterior left atrial adipose tissue might contribute to the structural and electric remodeling leading to the onset of AF. Adipocyte infiltration within atrial cardiomyocytes determines the loss of side-to-side cells connection with consequent reduced and heterogeneous voltage in posterior left atrium [78]. According with those evidence, EAT co-localizes with high dominant frequency areas and is significantly associated with P wave abnormalities. As an additional mechanism, an increased EAT volume may alter the function of ganglioned plexi, located near the pulmonary veins [79]. On the other hand, the closed proximity of EAT to atrial cardiomyocytes might favor the paracrine activity of EAT secretome. The release of pro-fibrotic factors (i.e. matrix metalloproteinases and transforming growth factors) determines the interstitial expansion of myocyte bundles, thus promoting the electrophysiological remodeling of the atria. EAT is also a relevant source of adipocytokines (e.g. IL-1β,

Table 2
Studies reporting an association between epicardial adipose tissue (EAT) and heart failure.

Author	Year	Study design	EAT measure	Outcome
Doesch et al. [63]	2010	Cross-sectional 66 patients with CHF and 32 healthy controls undergoing CMR	EAT volume	EAT increased with increasing with LVEDD ($r = 0.420$; $p < 0.001$) and LVEDM ($r = 0.590$; $p < 0.001$). However, the EAT mass/LVEDM ratio was significantly reduced in patients with CHF compared to healthy controls ($p < 0.001$).
Cetin et al. [64]	2013	Cross-sectional 127 hypertensive patients undergoing TTDE	Mean EAT thickness	EAT was significantly correlated with left atrial dimension, LV mass and LVDD. EAT was significantly increased in patients with high grades LVDD ($p = 0.001$). Linear regression analyses revealed EAT as an independent predictor of LVDD parameters: E/A ration IVRT, MPI and LA volume ($p < 0.001$; $p = 0.045$, $p < 0.001$ and $p = 0.023$, respectively). The AUC values of EAT for the presence and degree of LVDD were 0.749 and 0.630, respectively.
Nyman et al. [65]	2013	Case-control 37 men with and 38 men without MetS undergoing CMR	EAT volume	EAT was greater in the MetS than in the control group ($p < 0.001$). LVDD was associated with MetS and inversely correlated with EAT ($r = 0.279$; $p < 0.05$).
Park et al. [66]	2014	Cross-sectional 346 MetS patients undergoing TTDE	EAT volume	In subjects with MetS, EAT was significantly correlated with LVDD, even after adjusting for other cardio-metabolic risk factors (OR 1.85 [95% CI 1.15–2.95]; $p = 0.011$).
Vural et al. [71]	2014	Case-control 63 patients undergoing TTDE	EAT volume	Mean EAT was lower in patients with ventricular diastolic function 114.1 vs. 164.4 cm^3 ($p < 0.001$).
Fontes-Carvalho et al. [45]	2014	Cross-sectional 225 patients with recent (1 month) MI	EAT volume	At adjusted analysis, increasing EAT was associated with decreased E′ velocity ($\beta = -0.11$ [95% CI −0.19 to −0.03]; $p < 0.010$) and increased E/E′ ratio ($\beta = 0.19$ [95% CI 0.07 to 0.31]; $p < 0.010$). EAT also increased with increasing LVDD ($p = 0.001$).
Watanabe et al. [68]	2016	Cross-sectional 62 elderly women with LVEF ≥ 60%	Mean EAT thickness	EAT thickness inversely correlated inversely with S′ ($r = -0.402$; $p = 0.001$) and TMAD% ($r = -0.585$; $p < 0.001$, respectively), but not with LVEF. These significant relationships were maintained in adjusted analysis.
Nakanishi et al. [69]	2017	Cross-sectional 372 patients undergoing TTDE	EAT volume	The frequency of deteriorated LVDD (defined as a ≥20% decrease in early diastolic mitral annular velocity) increased was EAT tertile (12.9%, 21.0%, and 25.8%, respectively; $p = 0.037$).
Topuz et al. [70]	2017	Case-control 85 severe CAD, 82 patients with non-significant CAD and 83 control patients	Mean EAT thickness	EAT thickness was higher in CAD groups and increased with CAD severity (p for trend <0.001). In multivariate analysis, mea EAT thickness was also significantly associated with LVDD in control patients (OR 1.02 [95% CI 1.01–1.03], $p < 0.001$).

TTDE: transthoracic Doppler echocardiographic examination; LVDD: left ventricular diastolic dysfunction; MetS: metabolic syndrome; OR: odds ratio; CI: confidence interval; CAD: coronary artery disease; CMR: cardiovascular magnetic resonance; IVRT: isovolumetric relaxation time; MPI: myocardial performance index; LA: left atrial; AUC: area under the curve; LVEF: left ventricular ejection fraction; CHF: chronic heart failure; LVEDM: left ventricular and-diastolic mass.

IL-6, TNFα, MCP-1) and ROS, both exerting detrimental local effects on atrial myocardium.

9. Imaging quantification of epicardial adipose tissue

EAT quantification may be relatively easily assessed by a variety of different imaging techniques. Two-dimensional trans-thoracic echocardiography (TTE) is the most accessible and safe procedure to EAT measurement [80]. Although limited to the EAT surrounding right ventricle, results from TTE examination are strongly related to those achieved by magnetic resonance imaging (MRI) ($r = 0.910$; $p = 0.001$). Furthermore, a value >5 mm has been suggested as the threshold to define as "increased" the EAT thickness in low-risk populations [81], whereas there are not consensus data in obese subjects. Technical advances in software analysis currently allow semi-automatic quantification of EAT, but echocardiographic determination of EAT thickness still remains biased by the low reproducibility. For this reason, computerized tomography (CT) and MRI, which were initially used as a complementary technique to echocardiography, are gaining a prominent position in light of their reproducibility, high spatial resolution and volumetric quantification. Cardiac Magnetic Resonance (CMR) is currently considered the gold standard for EAT quantification [82]. Both thickness and volume may be easily measured by CMR, especially once three-dimensional 3D-Dixon based CMR approach has been developed. Indeed, the use of cardiac synchronization and respiratory triggering has further increased CMR accuracy [35]. Nevertheless, the high costs and the high time expenditure for the procedure are still limiting the routinely use of CMR in clinical practice. Finally, CT provides the best sensitive and accurate EAT assessment due to the higher spatial resolution as compared to ultrasound and CMR. Regional EAT thickness and volume may be assessed and potentially correlated with coronary calcium score and degree of stenosis [83,84]. 3D images may be reconstructed with multi-detector-row CT (MDCT), further improving spatial resolution [85]. Although this technique is burdened by the exposure to ionizing radiation and the high costs, cardiac CT is probably the most used for clinical studies.

10. Future perspectives and conclusions

The anatomic location of EAT determines its unique relevance in cardiovascular biology. Far from being a mere storage tissue, EAT is characterized by a complex secretome, which is largely influenced by genetic, epigenetic and environmental factors. Unfortunately, the extent to which EAT volume and thickness are dependent of BMI and visceral adipose tissue is not yet known. Similarly, whether dysfunctional EAT has a causative role in CV diseases (e.g. atherosclerosis, HF and AF) still remains to be elucidated. The development of 3D imaging have paved the way for clarifying this relationship, whereas radio density assessment might contribute to identifying cellular characteristics of dysfunctional EAT. Beside the need to improve imaging assessment of EAT, it is important to clarify whether volume/thickness reduction and phenotype changes might confer cardio-protective activity to EAT. Many interventional studies have proven EAT as modifiable factor. EAT reduction may be achieved with weight loss induced by diet, bariatric surgery or pharmacological treatments. In moderate and severely obese patients, weight loss in response to lifestyle changes determines EAT reduction and cardio-protective effects. Those changes are also associated with increased in adiponectin/leptin ratio and reduction of pro-inflammatory cytokines. Similar results may be obtained also using pharmacological treatments. Glucagon-like peptide 1 (GLP-1) receptor are expressed in EAT and their pharmacological activation leads to EAT reduction in a weight loss-dependent way. Also intensive statin treatment has been described to reduce EAT volume independently of the degree of lipid lowering. It has been then suggested that anti-inflammatory pleiotropic activities of statins might have a role in EAT reduction. Future studies are needed to address many questions in this fascinating field of research.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] C.J. Lavie, A. De Schutter, P. Parto, E. Jahangir, P. Kokkinos, F.B. Ortega, et al., Obesity and prevalence of cardiovascular diseases and prognosis-the obesity paradox updated, Prog. Cardiovasc. Dis. 58 (2016) 537–547.

[2] A. Vecchie, F. Dallegri, F. Carbone, A. Bonaventura, L. Liberale, P. Portincasa, et al., Obesity phenotypes and their paradoxical association with cardiovascular diseases, Eur. J. Intern. Med. 48 (2018) 6–17.

[3] M.E. Piche, P. Poirier, I. Lemieux, J.P. Despres, Overview of epidemiology and contribution of obesity and body fat distribution to cardiovascular disease: an update, Prog. Cardiovasc. Dis. 61 (2018) 103–113.

[4] A. Elagizi, S. Kachur, C.J. Lavie, S. Carbone, A. Pandey, F.B. Ortega, et al., An overview and update on obesity and the obesity paradox in cardiovascular diseases, Prog. Cardiovasc. Dis. 61 (2018) 142–150.

[5] K.A. Britton, C.S. Fox, Ectopic fat depots and cardiovascular disease, Circulation 124 (2011) e837–e841.

[6] Y. Wu, A. Zhang, D.J. Hamilton, T. Deng, Epicardial fat in the maintenance of cardiovascular health, Methodist Debakey Cardiovasc. J. 13 (2017) 20–24.

[7] L. Sun, C. Liu, X. Xu, Z. Ying, A. Maiseyeu, A. Wang, et al., Ambient fine particulate matter and ozone exposures induce inflammation in epicardial and perirenal adipose tissues in rats fed a high fructose diet, Part Fibre Toxicol. 10 (2013) 43.

[8] M. Furuhashi, T. Fuseya, M. Murata, K. Hoshina, S. Ishimura, T. Mita, et al., Local production of fatty acid-binding protein 4 in epicardial/perivascular fat and macrophages is linked to coronary atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 825–834.

[9] R.I. Meijer, E.H. Serne, H.I. Korkmaz, D.L. van der Peet, M.P. de Boer, H.W. Niessen, et al., Insulin-induced changes in skeletal muscle microvascular perfusion are dependent upon perivascular adipose tissue in women, Diabetologia 58 (2015) 1907–1915.

[10] O.V. Gruzdeva, O.E. Akbasheva, Y.A. Dyleva, L.V. Antonova, V.G. Matveeva, E.G. Uchasova, et al., Adipokine and cytokine profiles of epicardial and subcutaneous adipose tissue in patients with coronary heart disease, Bull. Exp. Biol. Med. 163 (2017) 608–611.

[11] T. Tsuruda, J. Kato, K. Kuwasako, K. Kitamura, Adrenomedullin: continuing to explore cardioprotection, Peptides, 2018 https://doi.org/10.1016/j.peptides.2018.03.012.

[12] B. Gaborit, C. Sengenes, P. Ancel, A. Jacquier, A. Dutour, Role of epicardial adipose tissue in health and disease: a matter of fat? Compr. Physiol. 7 (2017) 1051–1082.

[13] L. Liberale, F. Dallegri, F. Montecucco, F. Carbone, Pathophysiological relevance of macrophage subsets in atherogenesis, Thromb. Haemost. 117 (2017) 7–18.

[14] V.B. Patel, J. Mori, B.A. McLean, R. Basu, S.K. Das, T. Ramprasath, et al., ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity, Diabetes 65 (2016) 85–95.

[15] V.B. Patel, J.N. Lezutekong, X. Chen, G.Y. Oudit, Recombinant human ACE2 and the angiotensin 1-7 axis as potential new therapies for heart failure, Can. J. Cardiol. 33 (2017) 943–946.

[16] Y. Hirata, M. Tabata, H. Kurobe, T. Motoki, M. Akaike, C. Nishio, et al., Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue, J. Am. Coll. Cardiol. 58 (2011) 248–255.

[17] T. Kitagawa, H. Yamamoto, K. Sentani, S. Takahashi, H. Tsushima, A. Senoo, et al., The relationship between inflammation and neoangiogenesis of epicardial adipose tissue and coronary atherosclerosis based on computed tomography analysis, Atherosclerosis 243 (2015) 293–299.

[18] A.F. Grosso, S.F. de Oliveira, L. Higuchi Mde, D. Favarato, L.A. Dallan, P.L. da Luz, Synergistic anti-inflammatory effect: simvastatin and pioglitazone reduce inflammatory markers of plasma and epicardial adipose tissue of coronary patients with metabolic syndrome, Diabetol. Metab. Syndr. 6 (2014) 47.

[19] A. Baroja-Mazo, F. Martin-Sanchez, A.I. Gomez, C.M. Martinez, J. Amores-Iniesta, V. Compan, et al., The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response, Nat. Immunol. 15 (2014) 738–748.

[20] V.B. Patel, S. Shah, S. Verma, G.Y. Oudit, Epicardial adipose tissue as a metabolic transducer: role in heart failure and coronary artery disease, Heart Fail. Rev. 22 (2017) 889–902.

[21] M. Renovato-Martins, M.E. Matheus, I.R. de Andrade, J.A. Moraes, S.V. da Silva, M. Citelli Dos Reis, et al., Microparticles derived from obese adipose tissue elicit a pro-inflammatory phenotype of CD16(+), CCR5(+) and TLR8(+) monocytes, Biochim. Biophys. Acta 1863 (2017) 139–151.

[22] C. Li, S. Li, F. Zhang, M. Wu, H. Liang, J. Song, et al., Endothelial microparticles-mediated transfer of microRNA-19b promotes atherosclerosis via activating perivascular adipose tissue inflammation in apoE(−/−) mice, Biochem. Biophys. Res. Commun. 495 (2018) 1922–1929.

[23] A. Fernandez-Trasancos, R.M. Agra, J.M. Garcia-Acuna, A.L. Fernandez, J.R. Gonzalez-Juanatey, S. Eiras, Omentin treatment of epicardial fat improves its anti-inflammatory activity and paracrine benefit on smooth muscle cells, Obesity (Silver Spring) 25 (2017) 1042–1049.

[24] N. Nerlekar, A.J. Brown, R.G. Muthalaly, A. Talman, T. Hettige, J.D. Cameron, et al., Association of epicardial adipose tissue and high-risk plaque characteristics: a systematic review and meta-analysis, J. Am. Heart Assoc. 6 (2017) https://doi.org/10.1161/JAHA.117.006379.

[25] J. Mancio, D. Azevedo, F. Saraiva, A.I. Azevedo, G. Pires-Morais, A. Leite-Moreira, et al., Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis, Eur. Heart J. Cardiovasc. Imaging 19 (2018) 490–497.

[26] J.S. Park, S.Y. Choi, M. Zheng, H.M. Yang, H.S. Lim, B.J. Choi, et al., Epicardial adipose tissue thickness is a predictor for plaque vulnerability in patients with significant coronary artery disease, Atherosclerosis 226 (2013) 134–139.

[27] K. Yamashita, M.H. Yamamoto, S. Ebara, T. Okabe, S. Saito, K. Hoshimoto, et al., Association between increased epicardial adipose tissue volume and coronary plaque composition, Heart Vessel. 29 (2014) 569–577.

[28] K. Nakanishi, S. Fukuda, A. Tanaka, K. Otsuka, S. Jissho, H. Taguchi, et al., Persistent epicardial adipose tissue accumulation is associated with coronary plaque vulnerability and future acute coronary syndrome in non-obese subjects with coronary artery disease, Atherosclerosis 237 (2014) 353–360.

[29] M. Hassan, K. Said, H. Rizk, F. ElMogy, M. Donya, M. Houseni, et al., Segmental peri-coronary epicardial adipose tissue volume and coronary plaque characteristics, Eur. Heart J. Cardiovasc. Imaging 17 (2016) 1169–1177.

[30] R. Okubo, R. Nakanishi, M. Toda, D. Saito, I. Watanabe, T. Yabe, et al., Pericoronary adipose tissue ratio is a stronger associated factor of plaque vulnerability than epicardial adipose tissue on coronary computed tomography angiography, Heart Vessel. 32 (2017) 813–822.

[31] A. Senoo, T. Kitagawa, S. Torimaki, H. Yamamoto, K. Sentani, S. Takahashi, et al., Association between histological features of epicardial adipose tissue and coronary plaque characteristics on computed tomography angiography, Heart Vessel. 33 (2018) 827–836.

[32] A.A. Mahabadi, M.H. Berg, N. Lehmann, H. Kalsch, M. Bauer, K. Kara, et al., Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study, J. Am. Coll. Cardiol. 61 (2013) 1388–1395.

[33] E. Kunita, H. Yamamoto, T. Kitagawa, N. Ohashi, T. Oka, H. Utsunomiya, et al., Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography, Atherosclerosis 233 (2014) 447–453.

[34] G. Gitsioudis, C. Schmahl, A. Missiou, A. Voss, A. Schussler, H. Abdel-Aty, et al., Epicardial adipose tissue is associated with plaque burden and composition and provides incremental value for the prediction of cardiac outcome. A clinical cardiac computed tomography angiography study, PLoS One 11 (2016), e0155120. .

[35] R. Homsi, M. Meier-Schroers, J. Gieseke, D. Dabir, J.A. Luetkens, D.L. Kuetting, et al., 3D-Dixon MRI based volumetry of peri- and epicardial fat, Int. J. Cardiovasc. Imaging 32 (2016) 291–299.

[36] A.A. Mahabadi, N. Lehmann, S. Mohlenkamp, N. Pundt, I. Dykun, U. Roggenbuck, et al., Noncoronary measures enhance the predictive value of cardiac CT above traditional risk factors and CAC score in the general population, JACC Cardiovasc. Imaging 9 (2016) 1177–1185.

[37] A.A. Mahabadi, B. Balcer, I. Dykun, M. Forsting, T. Schlosser, G. Heusch, et al., Cardiac computed tomography-derived epicardial fat volume and attenuation independently distinguish patients with and without myocardial infarction, PLoS One 12 (2017), e0183514.

[38] M. Goeller, S. Achenbach, M. Marwan, M.K. Doris, S. Cadet, F. Commandeur, et al., Epicardial adipose tissue density and volume are related to subclinical atherosclerosis, inflammation and major adverse cardiac events in asymptomatic subjects, J. Cardiovasc. Comput. Tomogr. 12 (2018) 67–73.

[39] J.D. Morales-Portano, J.A. Peraza-Zaldivar, J.A. Suarez-Cuenca, R. Aceves-Millan, L. Amezcua-Gomez, C.H. Ixcamparij-Rosales, et al., Echocardiographic measurements of epicardial adipose tissue and comparative ability to predict adverse cardiovascular outcomes in patients with coronary artery disease, Int. J. Cardiovasc. Imaging 34 (2018) 1429–1437.

[40] F. Sen, S. Yilmaz, K.G. Balci, M. Gul, M.M. Balci, M.K. Akboga, et al., The relationship between epicardial adipose tissue thickness and infarct-related artery patency in patients with ST-segment elevation myocardial infarction, Angiology 67 (2016) 281–286.

[41] B. Balcer, I. Dykun, T. Schlosser, M. Forsting, T. Rassaf, A.A. Mahabadi, Pericoronary fat volume but not attenuation differentiates culprit lesions in patients with myocardial infarction, Atherosclerosis 276 (2018) 182–188.

[42] S.H. Kim, J.H. Chung, B.J. Kwon, S.W. Song, W.S. Choi, The associations of epicardial adipose tissue with coronary artery disease and coronary atherosclerosis, Int. Heart J. 55 (2014) 197–203.

[43] M. Obokata, T. Iso, Y. Ohyama, H. Sunaga, T. Kawaguchi, H. Matsui, et al., Early increase in serum fatty acid binding protein 4 levels in patients with acute myocardial infarction, Eur. Heart J. Acute Cardiovasc. Care 7 (2018) 561–569.

[44] I. Akoumianakis, C. Antoniades, The interplay between adipose tissue and the cardiovascular system: is fat always bad? Cardiovasc. Res. 113 (2017) 999–1008.

[45] R. Fontes-Carvalho, M. Fontes-Oliveira, F. Sampaio, J. Mancio, N. Bettencourt, M. Teixeira, et al., Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction, Am. J. Cardiol. 114 (2014) 1663–1669.

[46] L. Biere, V. Behaghel, V. Mateus, A. Assuncao Jr., C. Grani, K. Ouerghi, et al., Relation of quantity of subepicardial adipose tissue to infarct size in patients with ST-elevation myocardial infarction, Am. J. Cardiol. 119 (2017) 1972–1978.

[47] M. Horckmans, M. Bianchini, D. Santovito, R.T.A. Megens, J.Y. Springael, I. Negri, et al., Pericardial adipose tissue regulates granulopoiesis, fibrosis, and cardiac function after myocardial infarction, Circulation 137 (2018) 948–960.

[48] O. Gruzdeva, E. Uchasova, Y. Dyleva, D. Borodkina, O. Akbasheva, E. Belik, et al., Relationships between epicardial adipose tissue thickness and adipo-fibrokine indicator profiles post-myocardial infarction, Cardiovasc. Diabetol. 17 (2018) 40.

[49] S.D. Pierdomenico, A.M. Pierdomenico, F. Cuccurullo, G. Iacobellis, Meta-analysis of the relation of echocardiographic epicardial adipose tissue thickness and the metabolic syndrome, Am. J. Cardiol. 111 (2013) 73–78.

[50] S.W. Rabkin, The relationship between epicardial fat and indices of obesity and the metabolic syndrome: a systematic review and meta-analysis, Metab. Syndr. Relat. Disord. 12 (2014) 31–42.
[51] G. Iacobellis, Local and systemic effects of the multifaceted epicardial adipose tissue depot, Nat. Rev. Endocrinol. 11 (2015) 363–371.
[52] D.K. Song, Y.S. Hong, H. Lee, J.Y. Oh, Y.A. Sung, Y. Kim, Increased epicardial adipose tissue thickness in type 2 diabetes mellitus and obesity, Diabetes Metab. J. 39 (2015) 405–413.
[53] S. Baldasseroni, A. Pratesi, F. Orso, C. Di Serio, A. Foschini, A.G. Marella, et al., Epicardial adipose tissue and insulin resistance in patients with coronary artery disease with or without left ventricular dysfunction, Monaldi Arch. Chest Dis. 80 (2013) 170–176.
[54] C.H. Lau, S. Muniandy, Novel adiponectin-resistin (AR) and insulin resistance (IRAR) indexes are useful integrated diagnostic biomarkers for insulin resistance, type 2 diabetes and metabolic syndrome: a case control study, Cardiovasc. Diabetol. 10 (2011) 8.
[55] A. Salgado-Somoza, E. Teijeira-Fernandez, J. Rubio, E. Couso, J.R. Gonzalez-Juanatey, S. Eiras, Coronary artery disease is associated with higher epicardial retinol-binding protein 4 (RBP4) and lower glucose transporter (GLUT) 4 levels in epicardial and subcutaneous adipose tissue, Clin. Endocrinol. (Oxf.) 76 (2012) 51–58.
[56] A. Burgeiro, A. Fuhrmann, S. Cherian, D. Espinoza, I. Jarak, R.A. Carvalho, et al., Glucose uptake and lipid metabolism are impaired in epicardial adipose tissue from heart failure patients with or without diabetes, Am. J. Physiol. Endocrinol. Metab. 310 (2016) E550–E564.
[57] T.D. Wang, W.J. Lee, F.Y. Shih, C.H. Huang, Y.C. Chang, W.J. Chen, et al., Relations of epicardial adipose tissue measured by multidetector computed tomography to components of the metabolic syndrome are region-specific and independent of anthropometric indexes and intraabdominal visceral fat, J. Clin. Endocrinol. Metab. 94 (2009) 662–669.
[58] A.N. Aslan, T. Keles, H. Ayhan, H.A. Kasapkara, M. Akcay, T. Durmaz, et al., The relationship between epicardial fat thickness and endothelial dysfunction in type I diabetes mellitus, Echocardiography 32 (2015) 1745–1753.
[59] S. Darabian, J.Y. Backlund, P.A. Cleary, N. Sheidaee, I. Bebu, J.M. Lachin, et al., Significance of epicardial and intrathoracic adipose tissue volume among type 1 diabetes patients in the DCCT/EDIC: a pilot study, PLoS One 11 (2016), e0159958.
[60] M.J. Bakkum, I. Danad, M.A. Romijn, W.J. Stuijfzand, R.M. Leonora, I.I. Tulevski, et al., The impact of obesity on the relationship between epicardial adipose tissue, left ventricular mass and coronary microvascular function, Eur. J. Nucl. Med. Mol. Imaging 42 (2015) 1562–1573.
[61] C.J. Lavie, A. Sharma, M.A. Alpert, A. De Schutter, F. Lopez-Jimenez, R.V. Milani, et al., Update on obesity and obesity paradox in heart failure, Prog. Cardiovasc. Dis. 58 (2016) 393–400.
[62] T.B. Horwich, G.C. Fonarow, A.L. Clark, Obesity and the obesity paradox in heart failure, Prog. Cardiovasc. Dis. 61 (2018) 151–156.
[63] C. Doesch, D. Haghi, S. Fluchter, T. Suselbeck, S.O. Schoenberg, H. Michaely, et al., Epicardial adipose tissue in patients with heart failure, J. Cardiovasc. Magn. Reson. 12 (2010) 40.
[64] M. Cetin, S.A. Kocaman, M.E. Durakoglugil, T. Erdogan, E. Ergul, S. Dogan, et al., Effect of epicardial adipose tissue on diastolic functions and left atrial dimension in untreated hypertensive patients with normal systolic function, J. Cardiol. 61 (2013) 359–364.
[65] K. Nyman, M. Graner, M.O. Pentikainen, J. Lundbom, A. Hakkarainen, R. Siren, et al., Cardiac steatosis and left ventricular function in men with metabolic syndrome, J. Cardiovasc. Magn. Reson. 15 (2013) 103.
[66] H.E. Park, S.Y. Choi, M. Kim, Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography, BMC Cardiovasc. Disord. 14 (2014) 3.
[67] M. Vural, A. Talu, D. Sahin, O.U. Elalmis, H.A. Durmaz, S. Uyanik, et al., Evaluation of the relationship between epicardial fat volume and left ventricular diastolic dysfunction, Jpn. J. Radiol. 32 (2014) 331–339.
[68] K. Watanabe, T. Kishino, J. Sano, T. Ariga, S. Okuyama, H. Mori, et al., Relationship between epicardial adipose tissue thickness and early impairment of left ventricular systolic function in patients with preserved ejection fraction, Heart Vessel. 31 (2016) 1010–1015.
[69] K. Nakanishi, S. Fukuda, A. Tanaka, K. Otsuka, H. Taguchi, K. Shimada, Relationships between periventricular epicardial adipose tissue accumulation, coronary microcirculation, and left ventricular diastolic dysfunction, Can. J. Cardiol. 33 (2017) 1489–1497.
[70] M. Topuz, A. Dogan, The effect of epicardial adipose tissue thickness on left ventricular diastolic functions in patients with normal coronary arteries, Kardiol. Pol. 75 (2017) 196–203.
[71] B. Vural, F. Atalar, C. Ciftci, A. Demirkan, B. Susleyici-Duman, D. Gunay, et al., Presence of fatty-acid-binding protein 4 expression in human epicardial adipose tissue in metabolic syndrome, Cardiovasc. Pathol. 17 (2008) 392–398.
[72] G. Iacobellis, M.C. Zaki, D. Garcia, H.J. Willens, Epicardial fat in atrial fibrillation and heart failure, Horm. Metab. Res. 46 (2014) 587–590.
[73] D.S. Jiang, H.L. Zeng, R. Li, B. Huo, Y.S. Su, J. Fang, et al., Aberrant epicardial adipose tissue extracellular matrix remodeling in patients with severe ischemic cardiomyopathy: insight from comparative quantitative proteomics, Sci. Rep. 7 (2017) 43787.
[74] Y. Yang, S. Liu, R.Y. Zhang, H. Luo, L. Chen, W.F. He, et al., Association between C1q/TNF-related protein-1 levels in human plasma and epicardial adipose tissues and congestive heart failure, Cell. Physiol. Biochem. 42 (2017) 2130–2143.
[75] M. Packer, Leptin-aldosterone-neprilysin axis: identification of its distinctive role in the pathogenesis of the three phenotypes of heart failure in people with obesity, Circulation 137 (2018) 1614–1631.
[76] C.J. Lavie, A. Pandey, D.H. Lau, M.A. Alpert, P. Sanders, Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise, J. Am. Coll. Cardiol. 70 (2017) 2022–2035.
[77] D.H. Lau, U. Schotten, R. Mahajan, N.A. Antic, S.N. Hatem, R.K. Pathak, et al., Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications, Eur. Heart J. 37 (2016) 1573–1581.
[78] T. Zghaib, E.G. Ipek, S. Zahid, M.A. Balouch, S. Misra, H. Ashikaga, et al., Association of left atrial epicardial adipose tissue with electrogram bipolar voltage and fractionation: electrophysiologic substrates for atrial fibrillation, Heart Rhythm. 13 (2016) 2333–2339.
[79] K. Takahashi, Y. Okumura, I. Watanabe, K. Nagashima, K. Sonoda, N. Sasaki, et al., Anatomical proximity between ganglionated plexi and epicardial adipose tissue in the left atrium: implication for 3D reconstructed epicardial adipose tissue-based ablation, J. Interv. Card. Electrophysiol. 47 (2016) 203–212.
[80] G. Iacobellis, F. Assael, M.C. Ribaudo, A. Zappaterreno, G. Alessi, U. Di Mario, et al., Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction, Obes. Res. 11 (2003) 304–310.
[81] A.G. Bertaso, D. Bertol, B.B. Duncan, M. Foppa, Epicardial fat: definition, measurements and systematic review of main outcomes, Arq. Bras. Cardiol. 101 (2013) e18–e28.
[82] R. Mahajan, P. Kuklik, S. Grover, A.G. Brooks, C.X. Wong, P. Sanders, et al., Cardiovascular magnetic resonance of total and atrial pericardial adipose tissue: a validation study and development of a 3 dimensional pericardial adipose tissue model, J. Cardiovasc. Magn. Reson. 15 (2013) 73.
[83] T.D. Wang, W.J. Lee, F.Y. Shih, C.H. Huang, W.J. Chen, Y.T. Lee, et al., Association of epicardial adipose tissue with coronary atherosclerosis is region-specific and independent of conventional risk factors and intra-abdominal adiposity, Atherosclerosis 213 (2010) 279–287.
[84] T.S. Polonsky, R.L. McClelland, N.W. Jorgensen, D.E. Bild, G.L. Burke, A.D. Guerci, et al., Coronary artery calcium score and risk classification for coronary heart disease prediction, JAMA 303 (2010) 1610–1616.
[85] E. Nagy, A.L. Jermendy, B. Merkely, P. Maurovich-Horvat, Clinical importance of epicardial adipose tissue, Arch. Med. Sci. 13 (2017) 864–874.