Current Hypertension Reports (2019) 21: 36
https://doi.org/10.1007/s11906-019-0939-6

HYPERTENSION AND OBESITY (E REISIN, SECTION EDITOR)

Epicardial Adipose Tissue and Cardiovascular Disease

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Published online: 5 April 2019

Abstract

Purpose of Review Epicardial adipose tissue has been associated with the development/progression of cardiovascular disease. We appraise the strength of the association between epicardial adipose tissue and development/progression of cardiovascular diseases like coronary artery disease, atrial fibrillation, and heart failure with preserved ejection fraction.

Recent Findings Cross-sectional clinical and translational correlative studies have established an association between epicardial adipose tissue and progression of coronary artery disease. Recent studies question this association and underline the need for longitudinal studies. Epicardial adipose tissue also plays a definite role in the pathobiology of atrial fibrillation and its recurrence after ablation. In contrast to an early paradigm, epicardial adipose tissue does not appear to play a key role in the pathogenesis of heart failure with preserved ejection fraction in obese patients.

Summary The association of epicardial adipose tissue with atrial fibrillation is robust. In contrast, the association of epicardial adipose tissue with coronary artery disease and heart failure with preserved ejection fraction is tenuous. Additional research, including longitudinal studies, is needed to confirm or refute these proposed associations.

Keywords Epicardial adipose tissue · Coronary artery disease · Atrial fibrillation · Heart failure with preserved ejection fraction

Introduction

Visceral accumulation of adipose tissue (AT) is associated with systemic metabolic and inflammatory alterations that underlie the development of cardiovascular disease in obese subjects [1–3]. By convention, visceral AT (VAT) exclusively refers to omental and mesenteric accumulation of AT [4]. Continued caloric excess leads to VAT expansion and accumulation of AT in the space between the myocardium and the visceral pericardium thereby enlarging the normal epicardial AT (EAT) and altering its phenotype (Fig. 1) [5].

Cross-sectional clinical and translational correlative studies indicate that EAT expansion plays a role in the pathobiology of cardiovascular disease [6••]. Whether EAT role is independent from that of other ectopic AT depots and particularly VAT has not been thoroughly addressed in obese patients [7, 8••].

Partly due to its proximity with myocardium and coronary arteries, EAT is intuitively thought to play an important role in the pathobiology of coronary artery disease (CAD), atrial fibrillation (AF), and heart failure with preserved ejection fraction (HFpEF) [6••, 9]. However, investigations that support a role for EAT in the pathobiology of CAD, AF, and HFpEF rarely controlled for the presence of other ectopic AT depots, including VAT [10].

The aim of the present review is to provide a brief outline of the changing properties of EAT when it expands and a critical appraisal of the role of EAT in the pathobiology of CAD, AF, and HFpEF.

Epicardial Adipose Tissue

Epicardial AT lies between the myocardium and the visceral leaflet of the pericardium and mostly resides in the atrial-ventricular and inter-ventricular grooves and the major branches of the coronary arteries [11, 12••]. Age, waist circumference, ethnicity, and cardiac mass are independent determinants of EAT volume [13, 14]. The volume of EAT

This article is part of the Topical Collection on *Hypertension and Obesity*

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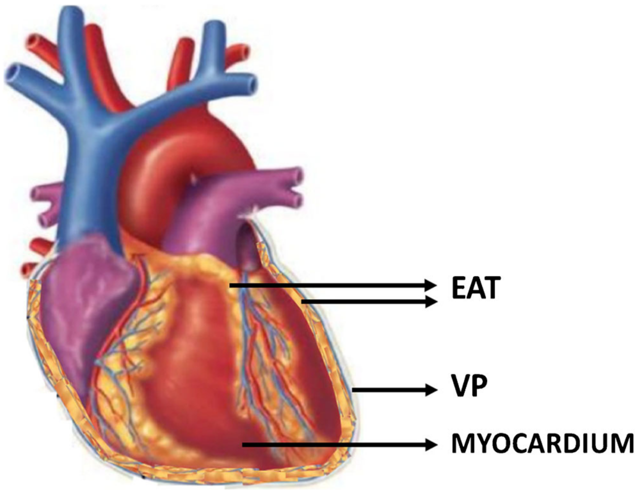

Fig. 1 Epicardial adipose tissue (EAT) refers to the adipose tissue that lies on the myocardial surface underneath the visceral pericardium in lean subjects. With continued caloric excess, EAT accumulates in the atrial-ventricular and inter-ventricular grooves. VP visceral pericardium

accounts for 15–20% of the normal heart volume and EAT mass 1% of the total AT mass [15]. The thickness of healthy EAT ranges from 5 to 7 mm over the right ventricular free wall and from 10 to14 mm in the atrial-ventricular and inter-ventricular grooves [16, 17]. In healthy lean subjects, the mass of EAT averages 100 g. The mass of EAT can increase to over 400 g in type 2 diabetic patients, occasionally reaching 800 g [18]. Of note, thickness and volume of EAT are rarely adjusted to body mass index (BMI), age, or cardiac muscle mass in clinical reports.

Epicardial and visceral AT have a common embryonic origin. Both originate from the splanchnopleuritic mesoderm, with EAT being vascularized by the coronary artery network [19••]. Human EAT consists of white AT with a greater expression of uncoupling protein 1 (UCP 1) than any other ectopic AT depot [12••]. Similar to brown AT, human EAT may have a role in thermo-regulation, thus protecting the heart against cold, and energy storage by supplying free fatty acids (FFA) to the myocardium [19••]. Other roles of EAT in humans are mechanical protection of the heart and coronary arteries, prevention of lipotoxicity by protecting the myocardium from high FFA levels, and immunological support [20]. When steadily expanding, VAT changes from a physiologic anti-inflammatory role that favors triglyceride storage to a pathophysiologic pro-inflammatory role that promotes the development of cardiovascular disease [21]. The visceral AT shift from a physiologic anti-inflammatory to a pathologic pro-inflammatory state was first uncovered in murine high-fat diet (HFD) models of obesity [22–24]. The lack of EAT in rodents precludes study of EAT in murine HFD models of obesity [25]. Further, the two-way interaction between EAT expansion and underlying myocardial/vascular alterations hinders the detection of any possible cause-effect relationship [19••, 26, 27].

Epicardial AT releases factors (adiponectin, leptin omentin-1, nitric oxide, palmitic acid methyl ester prostacyclin) that affect the myocardium and coronary vessels through paracrine (diffusion), vasocrine (via coronary vasa vasorum), or combined paracrine and vasocrine effects (Fig. 2) [28]. Release of exosomes carrying lipids, proteins, ribonucleic acids (RNAs), and microRNAs facilitate the cross talk between inflamed EAT and the coronary arterial wall [29]. Similarly to VAT and perivascular AT (PVAT), EAT exerts protective and anti-inflammatory properties in lean subjects [19••]. Epicardial AT is infiltrated by immune cells in obese subjects and releases less adiponectin and more leptin and omentin-1 in obese than in lean subjects [8••]. Enlarged and inflamed EAT may promote local inflammation, increase oxidative stress in the adjacent myocardium, and reduce myocyte contractile function through impaired intra-cellular Ca++ cycling [30].

In summary, as noted in VAT, the shift from an anti- to a pro-inflammatory phenotype may provide the mechanism by which EAT may trigger development/progression of cardiovascular disease.

Epicardial Adipose Tissue and Coronary Artery Disease

Shift Towards a Pro-inflammatory State

Epicardial AT expression of monocyte chemotactic protein-1, interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-α expression is high in patients with symptomatic CAD and BMI > 30 kg/m^2 [31]. In the absence of diabetes mellitus (DM) and obesity, pro-inflammatory mediators that are highly expressed in EAT surrounding the coronary arteries may mediate arterial inflammation through an outside-to-inside mechanism [31]. Epicardial AT-released adipokines can activate monocytes that promote atherogenesis through their effects on coronary endothelial and vascular smooth muscle cells [32]. Further, inflammation assessed by fluorodeoxyglucose F 18 uptake with positron emission computed tomography (FDG-PET) is greater in EAT than in any other AT locations and is particularly elevated in areas of coronary stenosis in patients with stable CAD [33]. Expression of CD68$^+$ macrophages is increased in EAT surrounding the left anterior descending coronary artery (LAD), and the LAD adventitia is infiltrated by CD68$^+$ cells in patients with obstructive CAD [34]. The ratio of classically activated to alternatively activated (M_1/M_2) macrophages and the expression of pro-inflammatory cytokines in EAT correlate with the severity of CAD [35]. The shift towards the M_1 macrophage phenotype is related to the loss of angiotensin (Ang)-converting enzyme (ACE)-2 and is associated with impaired adiponectin and fatty

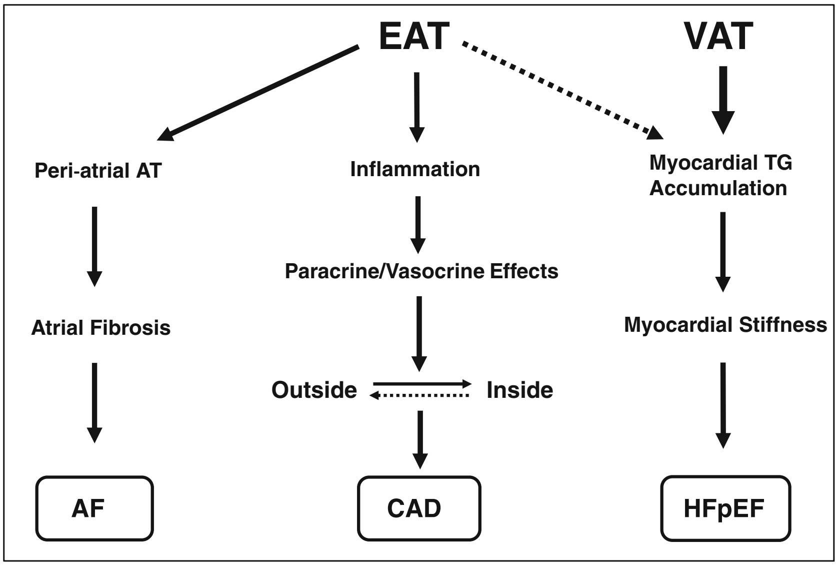

Fig. 2 Epicardial adipose tissue (EAT) contributes to the development/progression of atrial fibrillation (AF), coronary artery disease (CAD), and heart failure with preserved ejection fraction (HFpEF). EAT expansion leads to increased peri-atrial depot of adipose tissue that promotes atrial fibrosis and thereby AF. When expanding EAT becomes inflamed, it exerts paracrine/vasocrine effects that affect the coronary adventitia via the outside-to-inside pathway. Conversely, coronary atherosclerosis may affect EAT through the reverse inside to outside pathway. Myocardial accumulation of triglycerides (TG) affects left ventricular stiffness and thereby contributes to HFpEF. Visceral adipose tissue (VAT) and not EAT plays a major role in myocardial triglyceride accumulation

acid binding protein (FABP)-4 production [36]. Epicardial adipocytes are larger and express more Toll-like receptor − 2 and − 4 in CAD patients than in persons without CAD [37]. In symptomatic CAD patients, levels of IL-6, TNF-α, leptin, and vistafin are elevated in EAT, but to a lesser extent than in VAT [38]. Epicardial AT expression profiles of adiponectin, IL-1β, and $CD68^+$ cells correlate independently of each other with the severity of CAD [39]. Further, expression of nuclear factor-κB and c-Jun N-terminal kinase are increased in EAT from CAD patients compared to non-CAD patients [40].

Adipose tissue inflammation is frequently detected in perivascular tissue in the vicinity of stenotic coronary artery segments at time of coronary artery bypass (CABG) surgery in patients with extensive CAD. However, factors such as patient clinical characteristics and treatment modalities confound the interpretation of these findings [41]. Further, EAT inflammation may be either a contributor to the progression of coronary atherosclerosis or a result of advanced coronary artery disease.

Clinical Data

When measured perpendicularly to the right ventricle free wall at end of systole by transthoracic 2D-guided M-mode echocardiography, EAT thickness has been found to be associated with the presence and severity of CAD [42–44]. Further, EAT thickness has been reported to correlate with the presence of high-risk or unstable coronary plaques [45, 46]. In women without diabetes and obstructive CAD, increased EAT thickness has been associated with coronary microvascular impairment and a coronary blood flow reserve < 2 [47]. In contrast to the above studies, EAT thickness measured by echocardiography at the end of diastole has also been reported to be unrelated to the severity of CAD [48]. The poor reproducibility of 2D-guided M-mode echocardiography for EAT thickness measurement compared to multi-detector computed tomography (CT) likely accounts for these divergent findings [49]. The thickness of EAT by echocardiography also correlates poorly with EAT volume by CT [50].

When measured by CT, pericardial AT volume, which includes all AT around the heart, was found to be a stronger risk factor for CAD than VAT in both lean and obese (BMI > 25 kg/m^2) Japanese men [51, 52]. The Framingham Heart Study investigators found pericardial AT to be associated with coronary calcification and myocardial infarction after adjustment for obesity indices [53, 54]. Similarly, pericardial AT was found to predict incident CAD independent of conventional risk factors in the Multi-Ethnic Study of Atherosclerosis (MESA) [55]. Of note, in these early studies, pericardial AT referred to EAT plus pericardial AT, as EAT could not be reliably differentiated from pericardial AT [53, 54, 56]. Several single-center studies have reported a correlation between EAT volume and coronary atherosclerotic burden after adjustment for confounding factors, including VAT [56, 57]. In a series of studies, the Cedars Sinai investigators established a positive relationship between pericardial/epicardial AT burden and the presence and progression of coronary atherosclerosis in overweight (average BMI 28–29 kg/m^2) patients with and without known CAD [58–63]. Increased EAT volume has also been shown to be associated with insulin resistance and incident CAD in lean but not obese Japanese patients [64].

Two meta-analyses have more recently addressed the association between EAT volume and CAD [65, 66]. The first meta-analysis, involving 3772 patients enrolled in nine studies, only two of which accounted for VAT, concluded that increased EAT is associated with high-risk coronary atherosclerotic plaques [65]. The second meta-analysis of 70 studies involving 41,534 patients concluded that EAT volume was independently associated with obstructive CAD, myocardial ischemia, and major adverse cardiovascular events in low to intermediate cardiovascular risk subjects [66]. Surprisingly, EAT volume was associated with coronary artery calcification before but not after adjustment for markers of obesity, including BMI, waist circumference, and abdominal fat.

In contrast, recent studies failed to note an independent benefit of measuring EAT volume by CT for detection of obstructive CAD [67, 68••]. The first study that included 122 patients without a previous cardiac history showed that EAT volume measurements had no diagnostic value beyond calcium scoring and cardiovascular risk factors for the detection of obstructive CAD [67]. The second study that included 380 patients with known or suspected CAD showed that EAT volume was not associated with the presence or severity of CAD or myocardial perfusion abnormalities [68••]. EAT mass index to body surface area (EATMI) measured by CMR was identical in patients with ischemic and non-ischemic dilated cardiomyopathy [69]. The finding of identical EATMIs in patients with ischemic and non-ischemic cardiomyopathy argues against a major role of CAD in EAT expansion.

Following a plethora of clinical studies that supported a strong association between EAT volume and CAD presence and severity, more recent clinical studies are questioning the role of EAT in CAD pathobiology [67, 68••]. Studies of the role of EAT in CAD and PVAT in vascular pathology are attempting to answer a common question: Does inflamed ectopic AT trigger the development of coronary atherosclerosis/vascular disease or merely accelerate the progression of an underlying vascular process [70–72]?

Investigations of the role of EAT and of PVAT on CAD progression/vascular pathology share a common dilemna [70–72]. While studies suggest that PVAT inflammation and infiltration with macrophages and T cells precede atherosclerotic plaque development and impairment of nitric oxide endothelium-dependent bioavailability in ApoE$^{-/-}$ mice, a temporal relationship between EAT/PVAT inflammation and progression of coronary atherosclerotic lesions/vascular pathology remains to be ascertained in humans [73–75].

Epicardial Adipose Tissue and Atrial Fibrillation

Obesity, especially long-lasting obesity, increases the risk of developing AF by 50% [76–79]. For each kg/m^2 increment in BMI, the risk of incident AF increases by 3% for intermittent AF and 7% for sustained AF after adjustment for sex, age, and treated hypertension [79, 80]. Obesity-associated comorbid conditions such as hypertension (HTN), DM, CAD, HF, alcohol use, and obstructive sleep apnea (OSA) also predispose to the development of AF [81, 82]. Obese patients experience more left atrial (LA) remodeling and have greater LA filling pressure and lower LA contractility than normal weight patients after adjustment for obesity-associated conditions, including diabetes and OSA [83] and left atrial size is clearly the link between obesity and AF [79]. Sheep with fed a calorie-dense diet for 36 weeks develop sustained obesity but do not experience OSA [84••]. These obese sheep undergo global bi-atrial endocardial remodeling and LA enlargement with conduction abnormalities and interstitial fibrosis. Further, this obesity is associated with reduced posterior endocardial voltage and infiltration of posterior LA muscle by EAT. Atrial fibrillation is also associated with fibrotic remodeling of adipocytes that intermingle with right atrial appendage myocytes in humans [85].

Pericardial AT was associated with the prevalence of AF after adjustment for all AF risk factors (age, sex, HTN, valvular disease, BMI, and other ectopic AT depots) in the Framingham Heart Study [86]. The association between LA-EAT mass (indexed to body surface area in some studies) and AF was consistently corroborated after adjustment for all known risk factors for AF: age, sex, HTN, BMI, hyperlipidemia (HLD), DM familial history of CAD, and CAD [87–95]. Epicardial AT thickness between the esophagus and the LA posterior wall, the pulmonary artery and the LA anterior wall, and the descending aorta and the LA posterior wall is greater in patients with AF than in those in sinus rhythm [92••]. Epicardial AT between the esophagus and LA posterior wall is consistently thicker in patients with permanent than paroxysmal AF, [92••] and accounting for EAT thickness between the esophagus and LA posterior wall improves the predictive models of success with AF ablation. A meta-analysis of 63 observational studies involving 353,275 individuals ascertained that a 1-SD higher epicardial AT volume is associated with 2.6-fold higher odds of any AF, 2.1-fold higher odds of paroxysmal AF, and 5.4-fold higher odds of persistent AF compared to sinus rhythm [96••]. The strength of the association of AF with EAT is far greater than with abdominal or total AT [96••]. Further, EAT volume, indexed LA-EAT volume, and pericardial/epicardial AT thickness are major determinants of AF recurrence after ablation [87, 88, 93, 94, 97].

Women have less EAT than men overall, but postmenopausal women have a greater ratio of peri-atrial EAT to total EAT than age- and BMI-matched men [98]. The ratio of peri-atrial EAT to total EAT volume correlates with LA transport function in both post-menopausal women and in men. Post-menopausal women with AF have a lower LA transport function than age- and BMI-matched men [98]. The greater ratio of peri-atrial to total EAT volume and lower LA transport function in post-menopausal women than in age- and BMI-matched men likely contribute to the greater incidence of AF-related stroke in women [99, 100].

The changes in EAT volume/thickness after bariatric surgery (BAS) are highly variable and do not correlate with the changes in BMI [101–103]. A meta-analysis of 5 studies concluded that BAS does reduce EAT volume/thickness [104]. However, the reduction in EAT thickness was only 0.09 and 0.23 mm, respectively, in 2 of the studies. The variable effect of BAS on EAT may underlie the inconsistent effect of BAS on AF incidence [105–108].

In brief, the data that link EAT, particularly peri-atrial AT, to AF are robust. The association of AF with EAT is stronger than with other ectopic AT depots. The larger amount of peri-atrial AT in women may account for a lesser LA transport function and a greater incidence of AF-related stroke in women than in men.

Epicardial Adipose Tissue and Heart Failure with Preserved Ejection Fraction

After adjustment for age and blood pressure, obesity is associated with left ventricular (LV) concentric remodeling as evidenced by an increase in LV mass to volume ratio [109–111]. Concentric LV hypertrophy underlies the development of the HFpEF syndrome [111]. The obesity phenotype of HFpEF, first reported in African-American women 15 years ago [112, 113], is now a well-recognized phenotype of HFpEF that affects men and women of all ethnicities [111, 114, 115].

It has been reported that the severity of LV diastolic dysfunction (LVDD) is correlated with the volume of pericardial/epicardial AT after adjustment for BMI, waist circumference of both [116–119]. However, these studies did not measure or adjust their findings for VAT volume, a major determinant of LV function [120]. Few studies have measured VAT volume when assessing the relationship between pericardial/epicardial AT and LVDD or LV structure/function [121–124]. Fontes-Carvalho found that EAT volume and LVDD are correlated after adjusting for VAT. However, by quantifying VAT by area and EAT by volume, Fontes-Caravalho may have underestimated the impact of VAT on LVDD [121]. Fox correlated pericardial AT and LA volume (an indirect surrogate of LVDD) in women but not in men, after adjustment for VAT [122]. Finally, Graner et al. reported a correlation between LV end-diastolic volume-normalized peak filling rate and pericardial but not epicardial AT after adjustment for VAT [123]. Liu et al. noted that the association of pericardial AT with LVDD was not stronger than the association of VAT with LVDD [124]. Finally, a recent meta-analysis of 22 small and heterogeneous studies that rarely included measurement of VAT, not unexpectedly concluded that EAT volume correlates with myocardial diastolic function [125].

Two studies have specifically addressed whether EAT contributes to exercise intolerance in obese HFpEF patients [126, 127]. In the first report, epicardial AT thickness was measured by 2D-guided M-mode echocardiography and EAT volume was estimated from two hemi-ellipsoids containing atria and ventricles in the apical 4 chamber view [126]. Epicardial AT thickness was 7 mm (the upper limit of normal) in non-obese HFpEF controls and 10 mm in obese HFpEF patients. Corresponding EAT volumes were 797 ml and 945 ml in non-obese and obese HFpEF patients. Both EAT volumes were elevated and equal to or greater than maximal values previously reported [14]. As previously mentioned, CT and CMR provide more reliable quantification of EAT volume than echocardiography [49]. Surprisingly, despite a greater EAT volume in obese than non-obese HFpEF patients, atrial fibrillation was 2-fold more common in non-obese than obese HFpEF patients: 18 versus 9%. The exercise intolerance of obese HFpEF patients was attributed to EAT expansion that, in turn, may enhance passive pericardial restraint and ventricular interdependence.

In the second report, EAT volume was measured by CT in older HFpEF patients and healthy controls [127]. The volume of EAT was lower in older obese HFpEF patients than in healthy HFpEF controls, a finding that was later attributed to the metabolic demands of an energy-starved myocardium [128]. Of note, the paradigm of an energy-starved myocardium in older obese HFpEF patients was extrapolated from patients who, with advanced heart failure with reduced ejection fraction (HFrEF) and with decreased FFA utilization, run out of fuel [129–131]. In older obese HFpEF patients, increased FFA metabolism reduces mitochondrial efficiency, thereby lowering energy production [132]. Increased total (atrial + ventricular) EAT volume was recently reported in 64 HFpEF patients compared to 20 controls [133]. Of note, although 44% of HFpEF patients and none of the controls were in AF, atrial EAT volume was similar in HFpEF patients and controls. In contrast to the abundance of studies in CAD patients at the time of CABG surgery, the shift of EAT to a pro-inflammatory state has rarely been investigated in HFpEF patients, who rarely undergo cardiac surgery [36]. A novel metric of weighted CT attenuation may allow non-invasive detection of inflammation in EAT [134].

In summary, EAT-associated increase in pericardial restraint has modest effects, if any, on functional capacity and exercise hemodynamics in obese HFpEF patients, whereas increased pericardial/myocardial stiffness, impaired energetics, and myocardial accumulation of triglycerides mediate

LVDD in these patients (Fig. 2) [135••]. Pericardial/myocardial stiffness and reduced myocardial energetics account for 20 and 39%, respectively, of the effect of obesity on LV diastolic function. Myocardial accumulation of triglycerides (assessed by proton magnetic resonance spectroscopy [^{1}H-MRS]) accounts for the remaining 41% [135••]. However, VAT and not EAT is mainly responsible for myocardial accumulation of triglycerides in obese patients (Fig. 2), [136] and myocardial accumulation of triglycerides and myocardial fibrosis are more important mechanisms of LVDD than enhanced passive restraint [137–139].

Epicardial AT may contribute to myocardial dysfunction in HFpEF patients through mechanisms other than passive pericardial restraint and myocardial accumulation of triglycerides. The abundance of EAT around the coronary arteries may have a vasocrine effect in HFpEF patients by directly releasing vasoconstrictive molecules into the coronary arterial network [140]. Obesity and particularly EAT surrounding the coronary arteries may mediate microvascular inflammation that promotes endothelial dysfunction, impaired nitric (NO)-cyclic guanosine monophosphate (CGMP)-protein kinase G (PKG) signaling, and reduced coronary blood flow reserve [141••, 142–144]. Epicardial AT volume is also associated with a depressed response of the coronary microvasculature to sympathetic stimulation in healthy subjects [136]. In brief, EAT expansion may release vasoactive molecules that reach the microvascular network via coronary vasa vasorum in HFpEF and may limit myocardial blood flow during exercise.

As noted in patients with atrial fibrillation, EAT expansion is associated with LA dilation and impaired LA transport function [66, 98]. Left atrial conduit strain predicts peak aerobic capacity independent of LV stiffness and relaxation in obese HFpEF patients [145, 146]. Expanding EAT in HFpEF patients is likely to be associated with increased peri-atrial AT thickness, and thus, with further impairment of LA conduit function, increased LA strain and reduced exercise tolerance. Figure 2 summarizes various pathways by which EAT leads to CAD, AF, and HFpEF.

Conclusions

In conclusion epicardial AT volume and location play an important role in the pathobiology of AF. Peri-atrial AT impairs LA conduit function, increases thrombotic risk, and is a major cause of AF recurrence after ablation. Clinical studies that established an association between EAT volume/attenuation and CAD extent/severity were cross sectional, and translational studies were correlative. Longitudinal studies with targeted therapeutic interventions are needed to determine whether observed changes in EAT volume/attenuation result from or cause CAD development/progression. Impaired myocardial energetics and accumulation of triglycerides rather than enhanced passive pericardial restraint are major determinants of LVDD in obese patients. Myocardial accumulation of triglycerides correlates more closely with visceral than epicardial AT.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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

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