



Atrial Fibrillation and Epicardial Adipose Tissue

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Key Points

- Obesity has been associated with atrial fibrillation, while weight loss decreases atrial fibrillation (AF) burden and recurrence post-ablation.
- Epicardial adipose tissue is a risk factor for development of AF and predictor of recurrence after catheter ablation.
- The mechanism by which epicardial adipose tissue contributes to the pathogenesis of atrial fibrillation remains unclear. Various mechanisms have been proposed including fatty infiltration, fibrosis, inflammation, oxidative stress, atrial remodelling, and genetic factors.
- Peri-atrial epicardial adipose tissue (EAT) may play a more prominent role in the pathogenesis of AF due to its proximity to the atrial myocardium and local paracrine effect.

Introduction

Atrial fibrillation (AF) is linked with increased cardiovascular morbidity and mortality [1, 2]. AF is the most common sustained heart rhythm disorder affecting humans [3]. AF affects 5.2 million Americans as of 2010 with projections that it will affect 12.1 million people in the United States by 2030 [4]. Incremental cost related to AF has been estimated at \$6–26 billion per year in the United States alone [5]. This rise in AF prevalence is partially connected to a growing elderly population with AF prevalence doubling with each advancing decade of age >50 years [6, 7]. Besides age, various risk factors predispose to the development of AF, such as coronary artery disease [8, 9], obesity [10, 11], hypertension [6, 12–14], diabetes mellitus [15–17], heart failure, [6, 18], and sleep apnea [19–21].

As these risk factors do not directly affect the atrium, their association with AF is likely mediated by intermediate pathways causing disease in the atrial myocardium. Moreover, as in coronary artery disease, the clinical manifestation of AF is likely preceded by years of subclinical progressive atrial disease (atrial myopathy), which may involve inflammation, oxidative stress, fibrosis, and electrical, structural, and autonomic remodelling [22–26]. Multiple studies show that obesity is associated with the development of AF substrate via various mechanisms [27–30]. Obesity may contribute to the

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development of AF indirectly via its effects on comorbidities such as hypertension (activation of renin-angiotensin-aldosterone system) and obstructive sleep apnea (hypoxia and hypercapnia, systemic information). Obesity may also be directly implicated in the development of AF via local pro-inflammatory effects [27–30].

Obesity is associated with epicardial adipose tissue (EAT) [10, 31–46]. Due to its contiguity to the underlying atrial myocardium, it is possible that epicardial adipose tissue (EAT) is associated with the development of AF. In this chapter, we will explore the nature of the relation between EAT and AF, pathophysiological mechanisms, clinical correlation, and some proposed future therapeutic options targeting EAT.

Obesity and Atrial Fibrillation

The role of adipose tissue in multiple disease states has now been clearly established. Adipose tissue is a heterogeneous tissue that includes mature adipocytes, inflammatory cells of various phenotypic characteristics, fibroblasts, and stem cells as well as vascular cells coming from microvascular structures embedded in the tissue [47]. All cell types contribute to the adipose tissue secretome, which may contain pro-inflammatory and pro-atherogenic adipocytokines (e.g., resistin, leptin, visfatin, and monocyte chemoattractant protein-1) in metabolically unhealthy obesity [48]. The adipocytokines secreted by the adipose tissue can exert paracrine effects on the neighboring vascular wall (i.e., perivascular adipose tissue) [49] or myocardium (i.e., epicardial adipose tissue) [50], as well as endocrine effects (i.e., from “remote” depots like subcutaneous adipose tissue) on the cardiovascular system through the circulation [51].

The most widely used assessment of adiposity is weight/body mass index [52]. The population disease burden due to the obesity epidemic is widely recognized. Obesity rates worldwide have nearly tripled in the last 40 years, with more than a third of the world’s population being obese or overweight [53]. As for the United States, 38% of adults are obese, with a body mass index (BMI)

over 30 kg/m², and an additional 33% are overweight with BMI between 25 and 30 kg/m² [54]. In recent years, obesity has been shown to be an independent risk factor for development of AF (Table 10.1) [10, 31–46]. Importantly, the Framingham Heart Study revealed a 4% increased risk in incident AF per unit increase in body mass index in both men and women [31]. A meta-analysis of 51 studies involving more than 600,000 individuals evaluated the impact of obesity on AF [36]. It was found that every 5-unit rise in BMI confers an additional 19–29% risk of incident AF, a 10% risk of postoperative AF, and a 13% risk of post-ablation AF [36]. The association of obesity with other coexisting risk factors for AF (such as diabetes and hypertension) raises uncertainty in the independent association between obesity and AF. To account for this, Lee et al. recently conducted a retrospective study with a cohort of nearly 400,000 obese patients free of comorbidities [37]. The association between AF and obesity remained significant with a hazard ratio of 1.3 (95% confidence intervals 1.14–1.48) when compared to healthy non-obese patients [37]. Additionally, one study that followed 3248 patients for 5.1 years found that BMI independently predicted progression of AF from paroxysmal to permanent – hazard ratio of 1.04 (95% CI, 1.03–1.06; $P < 0.0001$) [38]. BMI was also shown to be an independent predictor of AF relapse post-ablation therapy in a recent multicenter observational study hazard ratio of 1.01 per kg/m² (95% CI, 1.01–1.02, $P = 0.002$) [39].

The impact of weight loss on AF is also well established and evident in multiple recent studies [55–60]. Abed et al. conducted a randomized, interventional clinical trial in Australia for overweight or obese patients (body mass index >27 kg/m²) with symptomatic AF. Patients were randomized into a structured weight management group (intervention) or general lifestyle advice (control) [55]. The interventional group showed a dramatic reduction in weight, AF symptom burden scores, symptom severity scores, and number of AF episodes when compared to control [55]. The Aggressive Risk Factor Reduction Study for Atrial Fibrillation (ARREST-AF) study [59] included a cohort of patients who underwent a structured risk

Table 10.1 Epidemiological studies showing association between obesity and atrial fibrillation

Study	Country	Study design	Population	Follow-up	Key findings for atrial fibrillation
Wang et al. [31]	USA	Community-based prospective observational study	<i>N</i> = 5282 Age 57 ± 13 years 55% female	13.7 years	AF adjusted HR 1.04 (95% CI, 1.01–1.04; <i>P</i> = 0.02) for men and 1.04 (95% CI, 1.01–1.07; <i>P</i> = 0.009) for women per unit increase in BMI
Frost et al. [10]	Denmark	Population-based prospective cohort	<i>N</i> = 47,589 Age 56 years (50–64) 53% female	5.7 years	Adjusted HR of 1.08 (95% CI, 1.05–1.11) for men and 1.06 (95% CI, 1.03–1.09) for women for AF/flutter per unit increase in BMI
Tedrow et al. [33]	USA	Prospective women's health study	<i>N</i> = 34,309 Age 54.6 ± 7.0 years 100% female	12.9 years	BMI was linearly associated with AF risk, with adjusted HR 1.04 (95% CI, 1.03–1.06)
Huxley et al. [40]	USA	Prospective The Atherosclerosis Risk in Communities study (ARIC)	<i>N</i> = 14,598 Age 54.2 ± 5.8 55% female	17.1 years	17.9% AF incident attributed to overweight and obesity
Long et al. [41]	China	Community-based nested case control study Giangzhou Biobank cohort study	<i>N</i> = 19,964 Age 62 years 71% female	2.9 years	Adjusted HR 1.06 (95% CI, 1.01–1.11 per unit increase in BMI)
Karasoy et al. [42]	Denmark	Prospective observational study	<i>N</i> = 271,203 Age 30.6 ± 4.7 years 100% female	4.6 years	Adjusted HR = 1.07 (95% CI, 1.04–1.11; <i>P</i> < 0.0001) per unit increase in BMI
Knuiman et al. [34]	Australia	Prospective observational study	<i>N</i> = 4267 56% female	15 years	Adjusted HR 1.34 (95% CI, 1.21–1.49; <i>P</i> < 0.0001) per 1 SD increase in BMI
Berkovitch et al. [43]	Israel	Prospective observational study	<i>N</i> = 18,290 Age 39 ± 11 years 73% male	6.4 years	Adjusted HR compared to normal weight 1.49 (95% CI, 1.11–2.00; <i>P</i> = 0.008) for overweight and 2.34 (95% CI, 1.64–3.34; <i>P</i> = 0.001) for obese
Lee et al. [37]	South Korea	Retrospective observational study	<i>N</i> = 389,321 Age 45.6 ± 11 years 27% female	7.5 years	Compared to non-obese HR for obesity 1.19 (95% CI, 1.12–1.27)
Foy et al. [44]	USA	Prospective observational cohort study	<i>N</i> = 67,278 76.9% female	8 years	Adjusted OR 1.40 (95% CI, 1.26–1.56) for obesity
Lim et al. [45]	South Korea	Korean National Health Insurance Service–Health Screening cohort	<i>N</i> = 171,324 39% female	47.4 months	Adjusted HR 1.01 (95% CI, 0.9–1.12; <i>P</i> = 0.85) for risk of new onset AF for BMI >25

AF atrial fibrillation, BMI body mass index, CI confidence interval, EAT epicardial adipose tissue, HR hazard ratio, OR odds ratio, PAF paroxysmal atrial fibrillation, PeAF persistent atrial fibrillation, PVI pulmonary vein isolation

factor management program following catheter ablation for treatment of AF in one arm, and a control group who did not participate in the risk factor management program in the second arm. Patients in the risk factor management program experienced a 13% decrease in body mass index (versus

1% for the control group) after a median follow-up of 42.8 months with significant decline in blood pressure and LA volume index [59]. Additionally, patients in this program after 2 years of follow-up achieved arrhythmia free survival at final follow-up of 32.9% (*P* < 0.001) after a single procedure and

87% ($P < 0.001$) after multiple procedures versus 9.7% ($P < 0.001$) for a single procedure and 17.8% ($P < 0.001$) for patients requiring multiple procedures in the control group [59]. The LEGACY study noted that weight loss $\geq 10\%$ resulted in six times greater probability of AF-free survival (95% confidence interval: 3.4–10.3; $P < 0.001$) compared to the groups with 3–9% and $< 3\%$ weight loss [60]. Moreover, the REVERSE-AF study assessed the progression and reversal of AF in the same cohort of the LEGACY study. In patients with $\geq 10\%$ weight loss, 88% experienced reversal from persistent to paroxysmal or no AF ($P < 0.001$) at final follow-up after individualized arrhythmia management, a striking difference when compared to 49% and 26% reversal in patients who lost 3–9% and $< 3\%$ of their body weight, respectively ($P < 0.001$) [58]. Despite the uncertainty of the exact mechanisms by which weight loss impacts AF, the evidence seems clear and strong. Hence, and for the first time, the 2019 focused update to the AF guidelines [61] introduced a class I recommendation: “For overweight and obese patients with AF, weight loss, combined with risk factor modification, is recommended” based on emerging data [36, 55, 59].

The mechanisms by which obesity impacts AF require investigation. In theory, obesity may directly (in addition to indirect effects through hypertension and diabetes) contribute to AF via systemic effects of visceral adiposity or from direct effects of the cardiac adipose tissue on the adjacent myocardium. The cardiac adipose tissue has been studied as the epicardial adipose tissue (EAT) or pericardial adipose tissue (PAT) and is associated with the development of AF (see Clinical Evidence of Association between EAT and AF) [62–66]. EAT is associated with increased body mass index (BMI) and is a well-documented risk factor for AF initiation and perpetuation [66–68]. EAT is a unique visceral adipose depot with anatomic and functional proximity to the myocardium and coronary arteries [69–72]. Advanced cardiac imaging has paved the way for better characterization of EAT and studying its effect on cardiovascular health [65, 73]. Under physiologic conditions, EAT has car-

dioprotective metabolic, thermogenic, and mechanical characteristics [70]. The pathophysiological mechanisms that link EAT to AF, however, remain elusive and are not entirely understood. Atrial electrical and structural remodeling, inflammation, oxidative stress, neural mechanisms, and genetic factors may be pathways mediating EAT effects on AF occurrence [22–26]. This will be discussed in the next section.

EAT and Atrial Fibrillation: Anatomy, Physiology, and Pathophysiological Mechanisms

Anatomy

EAT is a peculiar visceral fat depot with anatomical and functional contiguity to the myocardium and coronary arteries [69–72]. EAT is situated between the myocardium and visceral layer of the pericardium and is present in the atrioventricular and interventricular grooves without a structure or fascia separating it from the myocardium and the epicardial vessels [72, 74–76]. This means EAT and the myocardium share common microcirculation, suggesting a close and strong interaction between the two structures [77]. A paracrine process is one possible biological interaction between EAT and its adjacent myocardium. A vasocrine pathway is also likely via the vasa vasorum [72]. In contrast, pericardial adipose tissue is another cardiac fat deposit situated outside the visceral pericardium and on the outer surface of the parietal pericardium [77]. Although PAT and EAT are close in proximity, they are distinct [77]. Unlike EAT, PAT is separated from the myocardium by visceral pericardium [78]. PAT and EAT are also embryologically different [72]. EAT originates from the splanchnopleuric mesoderm, which also gives rise to mesenteric and omental fat [79], while PAT is derived from the primitive thoracic mesenchyme [79]. EAT is perfused by the coronary arteries, while PAT is supplied by a branch of the internal mammary artery, the pericardiophrenic artery [79]. However, it is

noteworthy that the effects of PAT rather than EAT on the heart are often reported [63–65, 80–84]. This likely relates to the methods of quantitation. A more detailed look at anatomy and terminology is described in Chap. 1.

Moreover, recent findings indicate that regional EAT distribution is important. Left atrial EAT (LAEAT) is significantly increased in patients with AF and may be related to the recurrence of AF after catheter ablation [65, 83, 85–89]. LAEAT displays a unique genetic pattern when compared to peri-coronary and peri-ventricular EAT [90]. LAEAT is enriched in genes involved in oxidative phosphorylation, muscular contraction, and calcium signaling when compared to other EAT areas [90].

Physiology

The functional complexity of human EAT is not yet fully understood. However, under physiological conditions, EAT's role in the heart is generally distinguished by mechanical, metabolic, thermogenic, and endocrine/paracrine functions [70]. EAT mechanically serves as a cushion protecting the coronary arteries from extreme distortion caused by arterial pulsation and myocardial contraction via its compressibility and elasticity [91]. Metabolically, EAT differs from other visceral fat in its ability to synthesize and break down free fatty acids (FFA) at a higher rate and a lower rate of glucose utilization [75, 92]. EAT contains abundant saturated fatty acids, and this enrichment and increased metabolism of free fatty acids (FFAs) maintain myocardial energy supplies, particularly during periods of high demand [71, 93]. FFA oxidation is responsible for about 50–70% of the energy production of the heart, and it is proposed that EAT functions as a buffer to protect the heart against excessively high levels of FFAs [72].

Moreover, EAT has higher expression of uncoupling protein-1 (UCP1) genes when compared to fat depots in other parts of the body [94]. This may provide EAT the thermogenic ability to produce heat (like brown adipose tissue) to protect the coronary arteries from hypothermia damage similar to what we see in hibernating animals

[75]. EAT also acts as a source for paracrine modulators of myocardial inflammation and oxidative stress by producing multiple bioactive cytokines [95]. Under normal physiological conditions, cytokines such as adiponectin and adrenomedullin have antidiabetic, antiatherogenic, antioxidative, and anti-inflammatory roles exerting cardioprotective functions [96–99]. This is discussed in detail in Chap. 2. However, despite its cardioprotective mechanisms, EAT in the pathological state can be harmful, producing inflammatory factors exacerbating cardiovascular diseases and may participate in the pathogenesis of AF via various mechanisms that will be discussed next.

Pathophysiological Mechanisms

Multiple studies have established an association between EAT and AF (see Clinical Evidence of Association between EAT and AF). However, the exact mechanisms by which EAT contribute to AF development are unresolved and remain an intriguing topic in translational research. Multiple mechanisms have been identified. These mechanisms could include a direct effect of EAT on the atrium (e.g., by the infiltration of adipose tissue into the myocardium leading to altered atrial electrophysiological properties) or indirect mechanisms (e.g., by acting as a source for paracrine modulators of myocardial inflammation and oxidative stress). Altered gene expression may play a role in the contribution of EAT to AF. Alternatively, EAT may influence local atrial and pulmonary vein electrophysiologic properties, such as the refractory period, which interact with a remodeled atrial substrate to sustain AF [100]. These mechanisms are discussed in detail below.

Fatty Infiltration

Given its location and the lack of fascia separating EAT from the underlying myocardium, direct fatty infiltration into the atrium is possible. Multiple previous studies have noted that the abundance of epicardial fat is associated with

direct adipocyte infiltration into the underlying atrial myocardium [78, 101]. This may contribute to myocardial functional disorganization and the formation of local arrhythmogenic substrate [102]. Mahajan et al., for example, found an accumulation of epicardial fat with pronounced myocardial infiltration by adipocytes, particularly over the posterior left atrial wall in diet-induced obese sheep [101]. In contrast, non-obese control sheep had less epicardial fat accumulation and minimal adipocyte infiltration into the myocardium. Such direct fatty infiltration can mechanically separate myocytes and could directly result in conduction slowing or could promote side-to-side cell connection loss similar to that seen with microfibrosis [103, 104]. Simultaneous endo-epicardial mapping of atrial electrical activity has shown that breakthrough and micro reentry circuits increase with increasing AF substrate complexity. Losing epicardial layer continuity due to atrial fibrosis appears to be one of the major determinants of the complexity of fibrillatory conduction pathways [105]. In addition to the direct anatomical effect of fatty infiltration, Haemers et al. [106] reported that patients with a history of AF had a higher histological degree of fibrosis of the adipose tissue present in sub-epicardium, with abundance of active inflammatory cells [106]. These observations suggest that this adipose tissue component of the atrial myocardium may not be an innocent bystander.

Inflammation

Inflammation is a potential contributor to the pathogenesis of AF. It may play a role in AF initiation and perpetuation [107]. Notable markers of inflammation, like C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1b (IL-1b), and tumor necrosis factor- α (TNF- α), have been associated with the incidence, severity, and recurrence of AF [108–112]. These markers are produced by EAT and may have local pro-inflammatory effects on the adjacent atrial myocardium that facilitate arrhythmogenesis. Aviles et al. first demonstrated that

elevated CRP predicted increased risk of developing AF in a large population-based prospective cohort including 5806 patients [111]. In another study, it was found that high levels of CRP were a predictor of arrhythmia recurrence after cardioversion [110]. Li et al. demonstrated that serum TNF- α blood levels were higher in patients with AF compared with those in sinus rhythm and in persistent and permanent AF compared with paroxysmal AF [113].

The immunohistochemistry of the left atrial appendage obtained from 16 patients during cardiac surgery showed immunologically active monocytes, and macrophages with abundance of inflammatory proteins like monocyte chemoattractive protein-1, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1 that were more expressed in the endocardium of patients with AF compared to those in sinus rhythm [114]. This supports the hypothesis of a local immunologic inflammatory response in the atrium of patients with AF [114]. Moreover, the neutrophil-to-lymphocyte ratio was also shown to be an independent predictor for non-valvular AF [115]. Interestingly, it was demonstrated that elevated levels of monocyte chemoattractant protein-1 were found to be associated with increased epicardial fat thickness [116]. A significant correlation was found between EAT thickness and neutrophil-to-lymphocyte ratio [117].

In addition, the inflammatory activity of EAT reflected by maximal standardized uptake value (SUV) of 18-fluorodeoxyglucose(FDG)-positron emission tomography (PET) which reflects glucose metabolism was found to be higher in patients with AF compared to controls, and inflammatory activity of EAT adjacent to the LA, atrioventricular groove, and left main artery was greater than in subcutaneous or visceral thoracic tissue [118]. Kusayama et al. [119] reported that inflammation of EAT around the LA, but not subcutaneous adipose tissue is related to the presence of paroxysmal AF.

In addition to pro-inflammatory cytokines, adipose tissue also secretes adiponectin, an adipocytokine with anti-inflammatory effects [120]. Kourliouros et al. conducted a study to investigate the role of adiponectin in the patho-

genesis of postoperative AF. Ninety patients undergoing coronary artery bypass graft (CABG) surgery had adiponectin level measured in serum and EAT. Increased levels of adiponectin were associated with sinus rhythm (SR) following surgery, thus reinforcing the inflammatory hypothesis in the pathogenesis of postoperative AF [121]. Moreover, an inverse relationship between adiponectin and LA size, independent of age, sex, insulin resistance, and left ventricular mass, has been reported, suggesting that adiponectin could influence atrial remodeling [122]. Taken together, if inflammatory pathways in peri-atrial adipose tissue are implicated in the pathogenesis of AF, this could be a potential future target for the prevention of AF. For example, intraoperative dexamethasone administration demonstrated significant protection against AF after cardiac surgery in one large clinical study [123]. A recent meta-analysis demonstrated that steroid therapy reduces the incidence of postoperative AF and the length of stay in the intensive care unit or in the hospital [124]. It is possible that the greatest benefit of anti-inflammatory interventions is limited to settings of inflammatory reaction due to tissue damage such as in cardiac surgery and catheter ablation. More studies are needed to elucidate the role of inflammation and the benefit of anti-inflammatory interventions in patients with AF.

Atrial Remodelling

Electrical Remodelling

Left atrial EAT can directly modulate electrical properties and ion currents of LA myocytes. When LA myocytes were incubated with epicardial adipocytes, they had longer action potential durations, a more-positive resting membrane potential, larger late sodium currents, L-type calcium currents, and transient outward potassium currents (I_{to}), but smaller delayed rectifier potassium and inward rectifier potassium (K_{ir}) currents than control LA myocytes [125]. In the clinical setting, epicardial fat was independently associated with atrial conduction time in a large population study

as indicated by P-wave indices [126]. Moreover, left atrial EAT was associated with lower bipolar voltage and electrogram fractionation in 30 patients assessed in sinus rhythm before AF ablation. Multivariate analysis for the potential nonlinear association between EAT and low voltage zones was significant with OR = 1.60 ($P < 0.001$) [127]. Another small study using a 3D merge process and dominant frequency left atrial map identified EAT locations to correspond to high dominant frequency during AF [128, 129]. These data suggest a possible role of EAT on AF electrophysiological substrate that requires further research.

Structural Remodeling

Another potential mechanism is the role of EAT in atrial structural remodeling. Atrial fibrosis is the hallmark of structural remodeling. Interstitial fibrosis leads to heterogeneity of conduction, which provides a substrate for AF [130]. Atrial fibrosis is the primary pathologic abnormality seen in AF-related structural remodeling, and the degree of fibrosis has clinical implications [116, 131]. EAT may contribute to atrial fibrosis by exerting a paracrine effect on the atrium secreting profibrotic cytokines [132] such as activin A and matrix metalloproteinases (MMP) [72, 78, 121, 133, 134].

Activin A is a member of the TGF- β superfamily. First recognized as an inducer of follicle-stimulating hormone release, activin A is a multifunctional cytokine expressed in various tissue types. A profibrotic effect of activin A has already been described for liver fibrosis [135–137]. In rats, the supplementation of culture media with recombinant human activin A-induced marked rat atrial myocardial fibrosis, while anti-activin A antibody neutralized these profibrotic effects [138]. Both EAT-conditioned medium and activin A induced the expression of TGF- β 1 and - β 2 in the atria, which could indirectly mediate the profibrotic effect of activin A [138]. Activin A-induced cardiac effects other than fibrosis have also been described. For instance, this cytokine has anti-hypertrophic and anti-apoptotic properties on the myocardium when it is exposed to ischemia, reperfusion, and pressure overload injuries [139, 140]. Activin A causes a negative inotropic effect on isolated

guinea pig cardiac myocytes, suggesting a direct effect of this cytokine on the excitation-contraction coupling process [141].

MMPs are important regulators of extracellular matrix homeostasis, including the various collagen fibers and basement membrane components. During AF, it has been demonstrated that upregulated activity of several MMPs, notably MMP2 and 7, contribute to the accumulation of interstitial fibrosis [142]. Levels of serum MMP2, which has been implicated in atrial remodeling, were higher in patients with greater EAT volume [143]. MMP8, which is abundantly expressed in EAT, is known to be involved in the formation of atherosclerotic plaques [144, 145], whereas little is known of its role in myocardial fibrosis [146]. Venteclef et al. found that the level of both activin A and MMP8 are enhanced in patients with heart failure. Moreover, Greulich et al. [139] report that activin A is more abundantly expressed in the EAT of obese patients with type 2 diabetes.

In a recent study, Wang et al. [147] showed that connective tissue growth factor (cTGF) expression is significantly higher in EAT than in subcutaneous or pericardial adipose tissue from patients with AF and in EAT from patients with sinus rhythm. They concluded that cTGF is associated with atrial fibrosis and can be an essential risk factor for AF [147].

EAT may also affect the atrial cellular components by altering the proliferation of myofibroblasts and the number of dedifferentiated and dystrophic myocytes [148, 149]. In fact, adipose tissue contains abundant stem cells located in the stroma fraction [150, 151] that are capable of differentiating not only into adipocytes but also into cardiomyocytes [152] or myofibroblasts [153]. Therefore, cardiac fatty tissue may constitute a source of precursor cells that can differentiate into myofibroblasts, contributing to atrial structural remodeling.

EAT may contribute to structural remodeling by promoting ventricular diastolic dysfunction. Patients with left ventricular diastolic dysfunction have a significant increase in EAT volume [154]. Suffee et al. [155] demonstrated that adult atrial epicardial progenitor cells can transition to adipocytes and provided evidence that this pro-

cess is driven by atrial natriuretic peptide (ANP) secreted by the myocardium. EAT accumulation in adult atria is a slow process that could occur in response to chronic alterations of atrial myocardium workload and metabolic conditions. Hence, these data indicate a possible crosstalk between EAT expansion and mechanical function of the atrial myocardium [155].

Oxidative Stress

EAT is known to be a source of reactive oxygen species that could contribute to the pathogenesis of AF [156]. Recently, Antonopoulos et al. [50] demonstrated that products of oxidation, such as 4-hydroxynonenal which is generated in the human cardiac tissue under conditions of increased oxidative stress, can act as signaling molecules and result in adiponectin upregulation in neighboring EAT. Adiponectin has a cardioprotective paracrine effect, and its upregulation is evidence of local defensive response of EAT against oxidative stress. Previous data have shown that the production of reactive oxygen species is higher in human EAT than it is in subcutaneous adipose tissue [156]. Ascorbat, an antioxidant and peroxyxynitrite decomposition catalyst, inhibited reactive oxygen species in dogs and appeared to attenuate atrial remodeling induced by rapid pacing [157].

Neural Mechanism

The autonomic nervous system plays an important role in the initiation and maintenance of AF. EAT is the anatomic site of the intrinsic cardiac autonomic nervous system, namely, ganglionated plexi (GP) and interconnecting nerves, especially in the posterior wall around pulmonary vein ostia [70]. These ganglia are a critical element responsible for the initiation and maintenance of AF [158, 159]. Sympathovagal imbalance detected by both impaired heart rate variability and heart rate turbulence parameters has been demonstrated to be related to EAT thickness [160]. Activation of the ganglionated plexi (GP)

located within the epicardial fat tissue can cause both parasympathetic and sympathetic stimulation, resulting in shortening of action potential duration and increases in calcium transient, respectively, in the atrial myocardium [161]. Recent evidence also suggests that it is the ganglionated plexi activity to the PVs that is important in the pathogenesis of AF [162]. One study demonstrated that stimuli applied to PVs do not induce AF, unless there is simultaneous stimulation of the adjacent GP that does not excite the atrial myocardium [163]. In isolated canine PV preparations, simultaneous administration of acetylcholine plus norepinephrine [164] or local autonomic (both parasympathetic and sympathetic) nerve electrical stimulation [165] has been shown to induce early after depolarizations (EADs) and short surges of triggered firing from the PVs, similar to the pattern recorded from the PVs in patients with paroxysmal AF [164].

Multiple clinical studies have investigated the role that neuromodulation may have in controlling AF, particularly by ablation of ganglionated plexi of the intrinsic cardiac nervous system [166]. It is possible that the encasing epicardial fat influences the ganglionated plexi and thus contributes to arrhythmogenesis. It is interesting to note that botulinum toxin injection into epicardial fat pads during surgery may reduce cardiac autonomic nervous activity and have long-term effects on AF, potentially by suppressing ganglionated plexi [167].

Genetic Factors

Gene expression represents a new perspective in understanding the precise role of EAT in AF pathogenesis. In an experimental study that utilized human and pig atrial samples, both AF and rapid pacing were associated with significant changes in atrial gene expression consistent with the induction of an adipocyte-related expression profile [168]. These genes favor the development of important risk factors for AF like obesity and diabetes mellitus and may facilitate AF substrate formation by increasing atrial ectopic fat and fat infiltration [168].

The peri-atrial EAT transcriptome profile is notable for the expression of genes implicated in oxidative phosphorylation, muscular contraction, and Ca²⁺ signaling [90]. The SERCA1 gene codes for a Ca²⁺/ATP-dependent intracellular pump that translocates the cytosolic Ca²⁺ into the lumen of the sarcoplasmic reticulum and promotes excitation-contraction coupling [169]. Moreover, EAT secretome was described as a possible substrate for postoperative AF [170]. It encompasses various proteins differentially expressed in patients who later develop postoperative AF. Among those, gelsolin reduction, a protein involved in inflammation and ion channel regulation, was associated with postoperative AF [170].

Clinical Evidence of Association Between EAT and Atrial Fibrillation

Several studies have described the association between cardiac adipose tissue and AF (Table 10.2) [64, 65, 80–82, 85, 86, 102, 171–174] and AF recurrence post-catheter ablation (Table 10.3) [65, 83, 85, 87–89, 175–179]. One of the largest studies that examined the relationship between pericardial fat and AF is from the Framingham Heart study. In this study involving 3217 participants, the investigators characterized pericardial fat (defined as adipose tissue within the pericardial sac) with computed tomography (CT) and observed that pericardial fat volume predicted AF risk independent of other measures of adiposity OR = 1.28 (95% CI, 1.05–1.6; *P* = 0.03) for every standard deviation increase in PAT volume [64]. This relation remained significant despite adjustment for common AF risk factors, including age, sex, myocardial infarction, heart failure, BMI, and other regional fat deposits [64]. Importantly, the study did not show similar association of AF with other fat deposits such as intrathoracic or abdominal visceral fat. This suggests that contiguity of adipose tissue rather than generalized increases in fat depots may be essential in the pathogenesis of AF [64].

Table 10.2 Studies showing association between epicardial and pericardial adipose tissue with atrial fibrillation

Study	Study design and location	Fat depot	Imaging	Population	Findings
Thanassoulis et al. [64]	Retrospective study Framingham Heart Study USA	PAT	CT	$N = 3217$ 54 AF	PAT associated with prevalent AF in multivariable-adjusted models OR 1.28 per SD of PAT volume (95% CI, 1.03–1.58; $P = 0.03$)
Batal et al. [171]	Retrospective study USA	LAEAT	CT	73 no AF 60 PAF 36 PeAF	LAEAT was a multivariate predictor of AF burden (OR 5.30; 95% CI, 1.39–20.24; $P = 0.015$)
Al Chekatie et al. [80]	Retrospective study USA	PAT	CT	76 no AF 126 PAF 71 PeAF	PAT multivariate predictor of PAF (OR = 1.11; 95% CI, 1.01–1.23, $P = 0.04$) and PeAF (OR 1.18, 95% CI, 1.05–1.33; $P = 0.004$)
Tsao et al. [85]	Retrospective study Taiwan	EAT	CT	34 no AF 68 AF	EAT increased in AF (29.9 ± 12.3 vs 20.2 ± 6.5 cm ³ ; $P < 0.001$)
Nagashima et al. [86]	Retrospective study Japan	EAT	CT	37 no AF 24 PAF 16 PeAF	Increased EAT and LAEAT in PAF vs no AF and PeAF vs PAF and no AF
Shin et al. [172]	Retrospective study South Korea	EAT	CT	80 no AF 40 PAF 40 PeAF	Increased EAT in PAF vs no AF and PeAF vs PAF and no AF
Wong et al. [65]	Retrospective study Australia	PAT	MRI	20 no AF 38 PAF 34 PeAF 30 permanent AF	PAT (OR 11.25; 95% CI, 2.07–61.24; $P = 0.005$) and peri-atrial fat (OR 5.35; 95% CI, 1.25–22.66; $P = 0.02$) are predictors of AF
Nakanishi et al. [173]	Retrospective study USA	EAT volume	CT	262 no AF 16 AF	Peri-atrial EAT a multivariate predictor of AF ($P < 0.001$)
Greif et al. [81]	Retrospective study Germany	PAT	CT	934 no AF 223 PAF 131 PeAF	PAT multivariate predictor of AF (OR 1.52; 95% CI, 1.14–2.00; $P = 0.03$) and of PeAF (OR 2.58; 95% CI, 1.69–3.99; $P < 0.001$)
Drossos et al. [82]	Prospective study Greece	PAT	CT	55 no AF 28 AF	PAT multivariate predictor of AF post-CABG (OR 1.018; 95% CI, 1.009–1.027; $P = 0.0001$)
Kanazawa et al. [174]	Prospective study Japan	PAT	CT	120 no AF 80 PAF 40 PeAF	PAT predictor of AF (OR 1.024; $P < 0.001$) and was independently associated with PeAF (OR = 1.018; $P < 0.018$)
Yorgun et al. [102]	Retrospective study Turkey	EAT Peri-atrial fat	CT	192 no AF 169 PAF 133 PeAF 124 permanent AF	EAT thickness were associated with AF (OR = 1.69; 95% CI, 1.54–2.85; $P = 0.002$) and peri-atrial fat associated with AF (OR 1.76; 95% CI, 1.35–3.22; $P = 0.001$)

AF atrial fibrillation, CI confidence interval, CT computed tomography, EAT epicardial adipose tissue, LA left atrial, OR odds ratio, PAF paroxysmal atrial fibrillation, PeAF persistent atrial fibrillation

Another study showed a correlation of pericardial adipose tissue with the severity of AF subtypes. Al Chekatie et al. [80] demonstrated that pericardial fat correlated with paroxysmal (OR = 1.11; 95% CI: 1.01–1.23, $P = 0.04$) and persistent AF (OR = 1.18; 95% CI: 1.05–1.33, $P = 0.004$), inde-

pendent of traditional AF risk factors including age, hypertension, sex, left atrial (LA) enlargement, valvular heart disease, left ventricular ejection fraction, diabetes mellitus, and BMI. This correlation was further confirmed in a recent meta-analysis that reported that EAT volume is associ-

Table 10.3 Studies showing association between epicardial and pericardial adipose tissue with atrial fibrillation recurrence post-catheter ablation

Study	Study design and location	Fat depot	Imaging	Population	Findings
Wong et al. [65]	Retrospective study Australia	PAT	MRI	20 no AF 38 PAF 34 PeAF 30 permanent AF	PAT predictive long-term AF recurrence post-ablation ($P = 0.035$)
Tsao et al. [85]	Retrospective study Taiwan	EAT	CT	34 no AF 68 AF	EAT multivariate predictor of AF recurrence after ablation ($P = 0.038$)
Murakami et al. [175]	Prospective study Japan	EAT	CT	32 PAF 6 PeAF	EAT a multivariate predictor of AF recurrence post-ablation (HR = 1.36; 95% CI, 1.10–1.66; $P < 0.004$)
Chao et al. [87]	Retrospective study Taiwan	EAT	TTE	227 PAF 56 non-PAF	Independent predictor of AF recurrence Non-PAF HR = 2.361 (95% CI, 1.4–3.98; $P < 0.001$) EAT thickness HR = 2.863 (95% CI, 2.11–3.88; $P < 0.001$)
Kim et al. [83]	Prospective study South Korea	PAT	CT	450 PAF 215 PeAF	PAT a significant predictor for AF recurrence post-ablation in PeAF (HR = 1.1; 95% CI, 1.05–1.16; $P < 0.001$)
Soucek et al. [176]	Prospective USA	EAT	CT	74 PAF 28 PeAF	EAT a predictive of 3 months AF recurrence after PVI (RR 1.01; 95% CI, 1.001–1.018; $P = 0.018$)
Kocyigit et al. [88]	Retrospective study Turkey	Peri-atrial EAT	CT	249 patients with AF	Peri-atrial EAT thickness multivariate predictor of late AF recurrence (HR 1.086; 95% CI, 1.037–1.137; $P = 0.001$)
Masuda et al. [89]	Prospective study Japan	EAT	CT	53 AF	Left atrial EAT multivariate predictor of early AF recurrence (OR 1.02; 95% CI, 1.01–1.03; $P < 0.003$)
Canpolat et al. [177]	Prospective study Turkey	EAT	TTE	190 PAF 44 PeAF	EAT thickness is a multivariate predictor of AF recurrence (HR 1.36; 95% CI, 1.10–1.66, $P < 0.004$)
Ciuffo et al. [178]	Prospective study USA	LA-peri-atrial fat	CT	143 AF	Higher LA-peri-atrial fat attenuation multivariate predictor of AF recurrence (HR 2.65; $P = 0.001$)
Mirollo et al. [179]	Retrospective study France	EAT	Cardiac MRI	231 AF	EAT a multivariate predictor of AF recurrence at 4 months (HR 1.96; 95% CI, 1.20–3.18; $P = 0.007$)

AF atrial fibrillation, CI confidence interval, CT computed tomography, EAT epicardial adipose tissue, HR hazard ratio, LA left atrial, MRI magnetic resonance imaging, OR odds ratio, PAF paroxysmal atrial fibrillation, PeAF persistent atrial fibrillation, PVI pulmonary vein isolation, RR risk ratio, TTE transthoracic echocardiogram

ated with increased risk of AF – one standard deviation was associated with 2.2 higher odds of persistent AF compared to paroxysmal AF (OR = 2.19, 95% CI: 1.66–2.88) [66, 68, 180]. Noteworthy, the strength of associations of AF with EAT was greater than for measures of abdominal or overall adiposity [66]. Increased EAT has also been independently associated with AF after coronary artery bypass grafting [82, 181], electrical cardioversion [182], or ablation [65, 83, 85–89, 176, 177,

183]. Moreover, pericardial fat, when measured by MRI in 130 patients, showed a strong dose-response association with LA volume ($P < 0.001$), AF chronicity ($P < 0.05$), symptom burden ($P < 0.05$), and recurrence of AF after ablation ($P = 0.035$) [65]. However, systemic measures of obesity, including body mass index and body surface area, were not associated with these outcomes. These associations remained valid despite multivariate adjustment and adjustment for body weight.

Recently, Shin et al. also reported that epicardial fat volumes and peri-atrial fat thickness measured by CT scan were significantly associated with the prevalence and persistence of AF [172]. Moreover, a multivariate analysis revealed that only total EAT ($P = 0.004$) and thickness of intraatrial septum ($P = 0.016$) were independently associated with left atrial volume in patients with AF even after adjusting for BMI. These studies have shown that EAT volume may be more predictive of the presence and severity of AF than the conventional measures of obesity.

It is important to note that EAT distribution is often asymmetric and may exert different effects according to its location [184, 185]. As mentioned earlier, it was found that peri-atrial epicardial fat has distinct characteristics and genetic profile compared to peri-ventricular or peri-coronary epicardial fat [90]. Hence, due to its proximity and unique genetic profile, it follows that peri-atrial epicardial fat may be more directly related to the pathogenesis of AF. This was observed in many studies that showed left atrial EAT was significantly increased in patients with AF and may be related to the recurrence of AF after catheter ablation [65, 83, 85–89, 171]. Batal et al. [171] examined 169 patients who underwent CT scans for AF or CAD, measuring EAT thickness. The study found posterior LA fat thickness was a statistically significant predictor of AF burden even after adjusting for age, BMI, or LA area OR = 5.30 (95% CI, 1.39–20.24; $P = 0.015$). On the other hand, what stands true for the left atrial EAT is not necessarily valid for right atrial EAT. Hasebe et al. [186] compared two groups of patients with paroxysmal AF referred for catheter ablation. They reported that EAT volumes around both the RA and LA in the patients whose AF was thought to originate from the RA were significantly smaller than those in the patients whose AF was thought to originate from the LA. Thus, EAT may be more involved in the pathogenesis of AF whose source is the LA. It is important to note that there was no statistical difference in the total volume of EAT surrounding the whole heart between the two groups.

Despite the inability of these studies to demonstrate causation, there is ample evidence of a strong association/correlation between EAT/PAT and AF. This opens the door for questioning about its future clinical implications.

Clinical Implications of EAT in Atrial Fibrillation and Possible Therapeutic Options

EAT as Risk Predictive Biomarker for Atrial Fibrillation

Epicardial adipose tissue is a novel risk prediction marker, and it may have multiple clinical applications in the future. EAT has been linked with various acute coronary syndrome risk prediction scores [187–190]. These include the GRACE (Global Registry of Acute Coronary Events) score, the Syntax score for the severity of coronary lesions, and the TIMI score for the prediction of adverse coronary events. They all have shown positive correlations with increased epicardial fat volume or thickness [187, 189, 191]. Similarly, an increased quantity of adipose tissue surrounding the heart has been shown to predict major adverse cardiac events, including myocardial infarction and death in subjects with acute coronary syndromes, as well as in those with suspected coronary artery disease [192–194]. Like in acute coronary syndromes, multiple studies have established an association between atrial fibrillation and EAT independent of coronary atherosclerosis and classical cardiovascular risk factors [195]. The pericardial adipose tissue was shown to be independently associated with the incidence, severity, recurrence of AF after catheter ablation, and poor ablation outcomes [65, 83].

EAT volume is also associated with stroke and adverse cardiovascular outcomes in AF patients. Akdag et al. [196] calculated the CHA₂DS₂-VASc score and baseline EAT thickness in 96 consecutive patients with AF and 52 age- and sex-matched controls and found that the group with high CHA₂DS₂-VASc score had higher EAT thickness compared to the group with low-intermediate CHA₂DS₂-VASc score;

the CHA₂DS₂-VASc score was positively correlated with EAT. Tsao et al. [197] evaluated whether EAT situated in the vicinity of the LA and the LA appendage (LAA) is correlated with atrial function and the subsequent development of AF-related stroke. They reported that increased accumulation of EAT (OR = 1.12, $P < 0.001$) around the LA was independently associated with stroke in AF patients [197]. Moreover, peri-atrial EAT was negatively correlated with the mechanical function of the LA (LAEF $r = -0.369$, $P < 0.001$). Total EAT was negatively correlated with active EF of the LAA ($r = -0.464$, $P < 0.001$). This contractile dysfunction and the circulatory stasis of the LAA may account for the pathophysiological association of EAT- and AF-related stroke [197]. Similarly, Chu et al. [198] demonstrated that increased EAT thickness per 1 mm is associated with adverse cardiovascular events (cardiovascular mortality, hospitalization for heart failure, myocardial infarction, and stroke) OR = 1.224 (95% CI, 1.096–1.368; $P < 0.001$). Moreover, the addition of EAT thickness to a model containing CHA₂DS₂-VASc score, LA volume index, and left ventricular systolic and diastolic function significantly improved the predictive value for cardiovascular events [198].

Potential Therapeutic Options Targeting EAT

Weight Loss

Weight loss has been recognized to reduce the pericardial fat burden [199]. Weight loss after bariatric surgery in obese subjects has also been associated with a decrease in EAT [200]. A recent meta-analysis showed a significant reduction in EAT with diet and bariatric surgery, but not with exercise [201]. Furthermore, in severe obesity, successful long-term weight reduction was associated with improved left ventricular diastolic function and exercise capacity, while reduction of epicardial fat thickness predicted improved diastolic function [202]. Sustained weight loss, as described in the ARREST-AF study [59] and LEGACY study [60], showed improved arrhyth-

mia free survival and substantial AF burden reduction. Whether a reduction in EAT mediates this effect, at least in part, remains unknown and requires further research.

Medications

Interestingly, statin therapy has been shown to decrease EAT. In hyperlipidemic post-menopausal women, statin therapy caused EAT regression, and intensive therapy was more effective than moderate-intensity therapy [203]. This, however, does not seem linked to low-density lipoprotein lowering and may be secondary to other actions of statins such as their anti-inflammatory effects [203]. A recent meta-analysis reported that perioperative statin therapy in patients with sinus rhythm undergoing cardiac surgery was associated with reduction in the development of postoperative AF, hospital length of stay, and CRP level [204]. This meta-analysis showed that the beneficial effects on AF and CRP were more marked in patients receiving atorvastatin compared to other statins [204]. Another meta-analysis showed that the use of statins is significantly associated with decreased risk of AF in patients with sinus rhythm, but did not examine changes in EAT [205]. Notably, the greatest benefit for statins was seen for postoperative AF prevention, as well as for secondary prevention of the arrhythmia [205]. Whether this effect is partially mediated by a decrease in EAT remains to be seen.

Antidiabetic medications may play a role in targeting EAT, leading to its reduction. In a study performed in type 2 diabetes patients, insulin replacement therapy resulted in a reduction of epicardial fat thickness [206]. EAT was recently collected from 9 patients during cardiac surgery, and it was found that human EAT expresses the GLP-1 receptor (GLP-1R) [207, 208]. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist; in an interventional case-controlled study, there was a rapid and substantial reduction in EAT thickness when liraglutide was given in addition to metformin vs metformin as monotherapy [209]. In the liraglutide plus metformin group, EAT thickness decreased by 29% and 36% ($P < 0.001$) at 3 and 6 months, respectively, whereas there was no

EAT reduction in the metformin group [209]. Liraglutide is currently being investigated as a potential pharmaceutical therapeutic option as adjunctive therapy to catheter ablation in the Liraglutide Effect in Atrial Fibrillation (LEAF) clinical trial (NCT03856632, <https://clinicaltrials.gov/>). It is proposed that liraglutide reduces EAT and may thereby stabilize the atrial substrate.

Conclusion

AF is a complex arrhythmia. The initiation and maintenance of AF are dependent on the presence of both trigger and substrate, including electrical and structural atrial remodelling. Obesity has been identified as an important modifiable risk factor for AF, and recent evidence showed that weight loss has a positive impact on AF. Given the growing prevalence of obesity and the expected rise in AF incidence in the future, it is essential to establish a better understanding of the pathogenesis of AF and find alternative therapy that can address the underlying substrate. EAT is also clearly associated with AF. It is reasonable to speculate that the association between obesity and AF may be mediated, at least in part, by EAT. Under pathological condition, EAT could contribute to the pathogenesis of AF via various mechanisms: fatty infiltration, inflammation, oxidative stress, atrial remodelling (electrical and structural), alterations in gene expression, and neuronal mechanisms. EAT could serve as a new risk predictive biomarker of atrial fibrillation and a potential therapeutic target in the future.

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