Atrial Fibrillation

Role of Epicardial Fat in Atrial Fibrillation
Pathophysiology and Clinical Implications

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ABSTRACT. Atrial fibrillation (AF) is the most common cardiac arrhythmia requiring treatment, but despite major research efforts devoted to AF, its pathogenesis is multifactorial and not yet fully understood. Epicardial fat has been an area of growing interest in understanding the pathophysiology of AF and its role in outcomes of AF treatment, particularly catheter and surgical ablation. Epicardial fat has been demonstrated to be a source of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1, and interleukin-6. It also secretes adiponectin, which has anti-inflammatory effects. The balance between pro-inflammatory and anti-inflammatory effects could be an important therapeutic target in AF. This review discusses the properties of epicardial fat, its role in pathogenesis of AF and outcomes of therapeutic modalities directed at epicardial fat.

KEYWORDS. atrial fibrillation, catheter ablation, epicardial fat.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice and the prevalence is increasing with age. It is an extremely costly public health problem, with hospitalizations as the primary cost driver (52%), followed by drugs (23%), consultations (9%), further investigations (8%), loss of work (6%), and paramedical procedures (2%). Globally, the annual cost per patient is close to US$3,600. AF is an important risk factor for stroke and is also associated with increased long-term risk of heart failure and all-cause mortality compared with sinus rhythm.

The pathogenesis of AF is complex, and there is increasing evidence supporting the mechanistic link between inflammation and AF. Inflammatory conditions such as pericarditis and myocarditis have been associated with AF. Atrial biopsies from patients with AF have shown evidence of increased inflammatory cells, further supporting the role of inflammation in the pathogenesis of AF. Epicardial adipocytes have been hypothesized to have arrhythmogenic properties by producing inflammatory cytokines, adipocytokines, and generating adipocyte–myocyte interactions which may contribute to AF. Epicardial fat is also postulated to exert a local effect by its proximity to the pulmonary vein ostia, which have known implications in AF pathogenesis.

Methods

We performed a comprehensive literature search in the PubMed database with the keywords “atrial fibrillation,” “epicardial fat,” “epicardial adipose tissue,” and “catheter ablation.” Original studies and clinical trials describing the
correlation between AF and epicardial fat were included. The language of clinical studies was restricted to English. Previously published reviews describing the role of epicardial fat in AF were not included as a primary reference source, but were used to identify additional studies of interest.

**Epicardial fat properties**

Epicardial fat is a form of visceral adipose tissue which is located between the myocardium and the pericardial parietal pericardium and shares a common embryonic origin with intra-abdominal adiposity, a fat depot believed to play an important role in metabolic syndrome.\(^{11,12}\) Observational clinical studies based on autopsy, magnetic resonance imaging (MRI) and echocardiography suggest that epicardial fat is more closely related to visceral fat than total fat.\(^{13,14}\) Epicardial fat can be used as an additional anthropometric parameter which can be conveniently measured by echocardiography and has an excellent correlation with MRI measurement of visceral adipose tissue. The presence of increased epicardial and visceral adipose tissue could reflect increased overall cardiovascular risk, which could further confer an increased predisposition to the development of AF. Inflammation may serve as a common link between epicardial fat, visceral fat, and the pathogenesis of AF. Both epicardial and visceral adipose tissue are important sources of interleukin (IL)-6 and monocyte chemoattractant protein-1, which are postulated to be key biochemical mediators of atrial fibrosis further leading to initiation and perpetuation of AF.\(^{15,16}\) A study by Corradi et al.\(^{13}\) identified a consistent association between ventricular epicardial fat and myocardial mass which was present in normal, hypertrophic, and ischemic hearts. Based on their study, it was concluded that a constant ratio of fat to muscle exists in each ventricle which is not influenced by ischemia or hypertrophy. As a result of the pro-inflammatory properties of epicardial fat, this association between epicardial fat and myocardial mass may explain, in part, the increased incidence of AF in patients with cardiac disorders that result in elevated myocardial mass.

**Biochemical properties of epicardial fat**

Various animal and human studies have been performed to study the biochemical properties of epicardial adipose tissue. A study on young adult guinea pigs demonstrated that epicardial fat has a high rate of free fatty acid synthesis, release, and breakdown, and also demonstrated that under normal physiologic conditions, epicardial adipose tissue acts as a buffering system against toxic levels of fatty acids between the myocardium and the local vascular bed.\(^{17}\) An increased amount of epicardial fat could lead to excess metabolism of fatty acids, which could lead to potentially arrhythmogenic metabolites.\(^{18,19}\) Epicardial tissue is demonstrated to be an important source of biochemicals that have a crucial role in vascular and immunologic response. These biochemicals exhibit cytokine-like characteristics and have been termed adipokines. Adiponectin is an important adipocyte-derived protein which has profound anti-inflammatory and antiatherogenic properties; it was demonstrated to be about 40% lower in patients with coronary artery disease than normal controls.\(^{20}\) The mechanism for the decreased adiponectin levels detected in patients with coronary disease has not been fully elucidated, but, given the anti-inflammatory properties of adiponectin, decreased levels may predispose to AF in these patients. In animal models, adiponectin has also been shown to bind to subendothelial collagen and thereby accumulates selectively at the site of the injured arterial wall. This could also suggest that adiponectin may act as an endogenous modulator for the vascular remodeling and repair process.\(^{21,22}\) It is also believed to be a key mediator of left atrial fibrosis and electrical remodeling. A study on 304 patients by Shimano et al.\(^{23}\) concluded that patients with persistent AF were found to have significantly increased plasma levels of adiponectin compared to patients with paroxysmal AF and controls. Given that adiponectin is believed to be protective in regard to the development of AF, this finding is counterintuitive. In their discussion, Shimano et al. speculate that this may reflect a disconnect between adiponectin levels and corresponding adiponectin receptor density, leading to increased adiponectin secretion. Resistin is another newly identified adipokine of great interest which is strongly linked with insulin resistance and has also been found to be increased in epicardial fat.\(^{24}\) Increased levels of resistin have also been demonstrated in diet-mediated obesity and genetic models of obesity. It is also believed to be a key link between metabolic signaling, inflammation, and atherosclerosis.\(^{25}\) In a prospective study on patients undergoing coronary artery bypass grafting (CABG), increased postoperative levels of plasma resistin were found to be associated with increased risk of development of AF.\(^{26}\) In a subset of the Framingham heart study, higher plasma concentrations of resistin were found to be related to increased risk of incident AF during up to 10 years of follow-up, after adjusting for traditional risk factors for AF\(^{27}\) (Table 1).

**Epicardial fat and AF pathogenesis**

Epicardial fat has been implicated in the pathogenesis of AF by multiple mechanisms. These mechanisms can be categorized into local effects which are mediated by the proximity of epicardial adipose tissue to the atrial wall and presence of ganglionated plexus and more distant effects. The epicardial adipose tissue is an important source of several pro-inflammatory cytokines and adipokines that are believed to be involved in the pathogenesis of AF.

**Local effects**

Studies aimed at investigating the pathogenesis of AF have demonstrated triggers that contribute to the
initiation of AF are frequently located in the pulmonary vein ostia. Epicardial fat is located in close proximity to the atrial wall, which may have direct atrial arrhythmogenic effects. An imaging study by Batal et al., investigated the relationship between the location of epicardial fat and AF burden. Epicardial fat was estimated on cardiac CT and measured (in centimeters) as the shortest distance between the mid-left atrium (LA) wall and three anatomic landmarks: esophagus (LA–ESO), main pulmonary artery (LA–PA), and descending thoracic aorta (LA–TA). LA–ESO (esophageal) periatrial fat was the only epicardial fat found to be associated with AF burden in this study. The esophagus follows a course along the posterior wall of the left atria and is frequently in close anatomic proximity to the pulmonary vein ostia. Local inflammatory mediators produced by the periatrial epicardial fat in the LA posterior wall may promote the activation of ectopic foci in the pulmonary vein ostia. A local arrhythmogenic effect of increased epicardial fat has also been suggested to be an important mechanism to explain obesity-related AF.

Complex fractionated atrial electrograms (CFAE) have been proposed to be a marker for AF drivers and substrate and are defined by sites of high frequency or continuous electrical activity during AF. Vagal nerves innervate the heart in a more autonomic tone has been implicated in the initiation and perpetuation of AF. Vagal nerves innervate the heart in a more heterogeneous manner than sympathetic nerves, and the resulting spatial heterogeneity may play an important role in pathogenesis of AF. Studies on patients with AF and experimental animal models have shown that stimulation of these ganglionated plexuses leads to markedly shortened action potential duration and increased calcium transient in pulmonary veins and the atrial myocardium, and can markedly influence the ability to generate and sustain AF. These ganglionated plexuses are epicardial structures in close apposition to epicardial fat, and could be influenced by local mediators secreted by this adipose tissue. Considering this mechanistic link, vagal denervation procedures have been performed experimentally in animal models and in patients with AF to determine whether denervation can improve the success rate of AF ablation.

### Inflammatory effects

Inflammation has been implicated as a key factor in the pathogenesis of AF. The role of inflammation has also been demonstrated in the setting of postoperative AF. inflammatory cytokines such as IL-6, tumor necrosis factor (TNF)-α and C-reactive protein (CRP) have been shown to play a key role in the pathogenesis and clinical course of AF. Monocyte chemoattractant protein-1 is another key pro-inflammatory molecule which has been implicated in the initiation of AF. Malavazos et al. demonstrated that elevated levels of monocyte chemoattractant protein-1 were found to be associated with increased epicardial fat thickness. A study by Kourliouros et al. on 90 patients undergoing CABG investigated the role of adiponectin in the pathogenesis of postoperative AF. Adiponectin was measured in serum and in epicardial adipose tissue; increased levels of adiponectin were found to be associated with sinus rhythm (SR) following surgery. The protective role of adiponectin could be possibly linked to its anti-inflammatory effects. Atrial fibrosis is the predominant pathologic abnormality seen in AF-related structural remodeling and the degree of fibrosis has clinical significance. Epididymal fat is a metabolically active tissue that generates a variety of bioactive molecules such as adiponectin and TNF-α, which could be the key mediators of structural remodeling and atrial fibrosis (Figure 1).

In a study using a rabbit model of heart failure and AF, eicosapentaenoic acid (EPA) was found to increase the expression and secretion of adiponectin and decrease TNF-α (a pro-inflammatory adipokine in the atrium and epicardial adipose tissue). Adiponectin could be a key mediator involved in the protective role of EPA in cardiac structural remodeling and attenuation of atrial fibrosis.

### Clinical assessment and implications of epicardial adipose tissue

Epicardial fat is readily visualized on transthoracic echocardiography (TTE), cardiac CT, and MRI; however,
the widespread use of these methods for its assessment is not routinely recommended in clinical practice. Patients with AF are likely to undergo cardiac imaging as a part of their routine clinical evaluation and before catheter ablation. TTE has been proposed as a useful modality for the assessment of epicardial fat.\textsuperscript{14,52} Epicardial fat is generally identified as the echo-free space between the myocardium and pericardium. Echocardiography could be applied as a simple method for further research in the quantification and characterization of epicardial fat.\textsuperscript{53} Cardiac CT can also be utilized for the measurement of epicardial fat, although it is typically more expensive than TTE, and it involves radiation exposure. Cardiac MRI has also been used to characterize the location and anatomical properties of epicardial fat (Figure 2). As discussed previously, epicardial fat pads are a common location of ganglionated plexuses, and autonomic denervation at these sites using either the epicardial or endocardial approach has been investigated for its impact on the success rate of catheter and surgical ablation of AF. Epicardial fat itself is relatively protected from current endocardial catheter ablation techniques, but catheter ablation can target the autonomic ganglia, and surgical procedures can target both epicardial fat and ganglia. Studies involving epicardial fat pad dissection and elimination (with associated autonomic denervation) in the setting of cardiac surgery have yielded conflicting results on the incidence of postoperative AF, and may depend on surgical technique.\textsuperscript{54–56} Given the close anatomic proximity of epicardial fat to autonomic ganglia, it is not possible to separate the relative contribution of each structure to clinical outcome with this type of surgical procedure.

Figure 1: Role of epicardial adipose tissue in the pathogenesis of atrial fibrillation.

Figure 2: T1 weighted fat-suppressed magnetic resonance imaging (250 μm resolution) of ex vivo human heart depicting location of epicardial fat.
Future therapeutic implications

Epicardial fat has generated interest in regard to its role in the pathogenesis of AF and as a novel therapeutic target for AF management. Further studies are needed to elucidate the mechanisms by which epicardial fat impacts AF. Identification of new biochemical mediators may help to better define the mechanisms involving epicardial adipose tissue contributing to the initiation and maintenance of AF. Regulation of the local pro-inflammatory and anti-inflammatory balance in the epicardial adipose tissue could be an important target for the treatment of AF.

References


