

# Interpretation of Epicardial Adipose Tissue Thickness and Heart Disease in Atrial Fibrillation Patients

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## *Abstract*

*Background:* Atrial fibrillation (AF) is commonly associated with overweight and obesity. Overweight populations have higher incidence, prevalence, severity, and progression of AF compared with their normal weight counterparts. Stable weight loss decreases AF burden and AF recurrence following treatment. Epicardial adipose tissue (EAT) is a small but very biologically active ectopic fat depot that surrounds the heart. Given its rapid metabolism, thermogenic capacity, unique transcriptome, secretory profile, and simple measurability, epicardial fat has drawn increasing attention among researchers attempting to elucidate its putative role in health and cardiovascular diseases.

*Keywords:* Atrial Fibrillation, Epicardial Adipose Tissue.

## **Atrial Fibrillation:**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. Patients are at increased risk of death, heart failure, hospitalization, and thromboembolic events (1).

The incidence of AF, similar to the prevalence, increases with advancing age (2).

In a longitudinal study in which 3983 male Air Force recruits were followed for 44 years, 7.5 percent developed AF (3).

## **Role of Left Atrium**

Emerging data suggest that the left atrium (LA) is much more than simply a conduit for left ventricular (LV) filling, and its size and remodeling are recognized as a predictor of poor outcomes in multiple disease states. LA dilation has been associated with increased risk of atrial fibrillation (AF), ischemic stroke, mortality after acute myocardial infarction, and heart failure with both reduced and preserved LV systolic function. In patients with heart failure, LA size provides incremental prognostic information over LV systolic and diastolic function (4).

The causal pathway linking LA size with adverse outcomes is not entirely clear, which highlights the fact that LA dilation can be multifactorial, resulting from valvular disease, systemic hypertension, and any condition causing elevated LV filling pressures. Furthermore, dilation itself predisposes to adverse outcomes, such as the development of AF and ischemic stroke. Hence, LA size may be considered a barometer for the combined effect of these conditions longitudinally (5).

The LA is a complex chamber with multiple functions, and it is important to recognize the dynamic relationship between LA and LV performance. The principal role of the LA is to modulate LV filling via its reservoir, conduit, and booster functions. During the reservoir phase, which is governed by LA compliance, the LA stores pulmonary venous return during LV

contraction and isovolumic relaxation. In the conduit phase, the LA passively transfers blood to the LV. Last, LA contraction during the booster phase in late diastole contributes about a quarter of LV stroke volume (6).

LA preload is largely volume dependent. The LA manifests adaptive changes in its structure and mechanics in response to changes in compliance of the LV, the primary determinant of LA afterload. These changes are well described in the setting of abnormal patterns of LV filling. Previous studies have shown that increasing LA volume and pressure leads to LA dilation with an initial increase in contractile function followed by worsening LA function with further dilation, similar to the Frank-Starling pressure volume relationship in the LV (6).

In the absence of mitral valve disease and AF, an increase in LA size most commonly reflects increased wall tension as a result of chronic elevation of LA pressure. This increase in LA size also results in impaired LA function due to atrial myopathy (6).

LA size has been found to be an important marker for the chronicity of elevated LV filling pressures and a powerful predictor of adverse cardiovascular outcomes, including stroke, development of AF, congestive heart failure, and death (5).

There are also data to suggest using LA size is a therapeutic target. Medical therapy with angiotensin-converting enzyme inhibitor and angiotensin-receptor blockers resulted in reverse remodeling and decrease in LA size (5). Therefore, accurate and reproducible measurement of atrial volumes is important in clinical practice.

### **Epicardial adipose tissue and heart disease**

It was first suspected in the 1960s and 1970s that atrial arrhythmias may be associated with excess adipose tissue within and surrounding the heart. There has been a growing interest in studying epicardial adipose tissue (EAT) over the last decade. Adipose tissue itself is now widely accepted to be an important endocrine and paracrine organ producing variety of active substances, which play a role in the development of obesity, metabolic syndrome and heart disease, especially coronary artery disease (CAD). It has inflammatory properties: both obesity and inflammation are risk factors for AF. In a study of 126 patients with AF and 76 controls, those with AF had a significantly higher epicardial fat volume (102 versus 76 ml) (7).

### **Role of EAT in heart disease**

The Framingham Heart Study and the MultiEthnic Study of Atherosclerosis found that the size of fat depots around the heart is independent risk predictors for cardiovascular dysfunction and CAD (8)

EAT volume and thickness were increased in patients suffering from CAD compared to patients with normal coronary arteries, and in patients with unstable angina as compared to patients with stable angina. Also EAT volume was larger in patients suffering from obstructive CAD and increased coronary artery calcium score. Authors suggest, that in patients with CAD, the EAT suffers greater oxidative stress than SAT (9).

### **Endocrine function of EAT**

Adipose tissue is well recognized as a dynamic endocrine organ producing a number of bioactive molecules that can affect not only energy metabolism, but also vascular, inflammatory and immunologic response. Several inflammatory and pro-atherogenic mediators, especially IL-6, IL-1 $\beta$  and TNF- $\alpha$  were significantly increased in EAT compared to plasma levels in patients with AS. These findings support the hypothesis of an involvement of ETA in atherogenic and inflammatory phenomena in the aortic valve and its promotion to calcific AS (10).

**Mazurek and colleagues (11)** found that epicardial adipose tissue expresses a wide range of inflammatory mediators. Epicardial fat had a significantly higher expression of monocyte chemoattractant protein-1 (MCP-1), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), interleukin-6 soluble receptor (IL-6 sr) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) than subcutaneous fat. Also, they further propose the hypothesis that the presence of inflammatory mediators, such as TNF- $\alpha$  in EAT around coronaries could amplify vascular inflammation, plaque instability and neovascularization. Other studies further demonstrated expression of numerous EAT adipokines, including adiponectin, omentin, adiponin, leptin, resistin, adrenomedullin, visfatin and chemerin. In particular, leptin, resistin and TNF- $\alpha$  have all diminished endothelial-dependent vasodilation, when administered experimentally (12).

### **Epicardial fat and atrial fibrillation**

Numerous studies support an association of epicardial fat with the presence of AF. In a CT analysis of 3217 individuals from the Framingham Heart Study, total epicardial fat volume was independently associated with prevalent AF. Similarly, in another CT series of 300 individuals by Al Chekatie and colleagues, total epicardial fat volume was also associated with prevalent AF (7). Batal and colleagues assessed 169 consecutive individuals with CT and found that peri-atrial epicardial fat thickness at the mid-left atrium was greater in patients with AF (13).

Population studies have demonstrated that body mass index, a measure of overall adiposity, is a strong predictor of AF. These data have shown that every 5 kg/m<sup>2</sup> increase in body mass index is associated with an approximate 10–30% higher risk of AF across a range of clinical settings. This association is particularly important in the context of progressive increases in global AF prevalence. It is estimated that AF will affect almost 18 million in Europe alone by 2060. The increasing impact of adiposity on these trends is driven by concurrently burgeoning obesity rates worldwide. Obesity already accounts for almost one-fifth of AF cases, and its population attributable-risk is likely to continue rising as developing countries undergo epidemiologic transition. Thus, these data underscore the central importance of adiposity as part of preventative and management strategies to reduce the public health burden of AF (14).

A range of pathophysiologic mechanisms could contribute to an association between epicardial fat and AF.

### **Probable mechanisms**

#### ➤ **Fatty infiltration**

Previous studies have noted that an abundance of epicardial fat is associated with direct adipocyte infiltration into the underlying atrial myocardium. In an ovine model, for example, sustained obesity led to the accumulation of epicardial fat with pronounced myocardial infiltration by adipocytes, particularly over the posterior left atrial wall (15).

In contrast, non-obese control animals had less epicardial fat accumulation and minimal adipocyte infiltration into the myocardium. Such direct fatty infiltration separating myocytes could directly result in conduction slowing or anisotropy akin to that seen with micro fibrosis (14)

Indeed, epicardial fat was independently associated with atrial conduction time in a large population study as indicated by P-wave indices. Direct fatty infiltration (and other potential mechanisms) may be further fueled by the inhomogeneous contact between patchy peri-atrial epicardial fat and the atrial myocardium, promoting conduction heterogeneity (15).

#### ➤ **Fibrosis**

It is increasingly appreciated that epicardial fat is a metabolically active tissue and a rich source of adipokines. Moreover, direct anatomic contiguity, adipocyte infiltration, and accumulation of

adipokines secreted from epicardial fat within the pericardial sac may facilitate paracrine effects on the atrial myocardium that promotes fibrosis. Supporting this theory is data demonstrating that secretome from human epicardial fat, but not from subcutaneous adipose tissue, has marked pro-fibrotic effects on rat atrial myocardium (16).

Furthermore, the adipokine activin A, a member of the TGF- $\beta$  superfamily secreted by epicardial fat, is able to reproduce such atrial fibrosis, an effect that can be blocked by anti-activin A antibodies (16).

It may be possible that other pro-fibrotic adipokines known to be secreted by epicardial fat may also contribute to remodeling of the atrial myocardium. For example, matrix metalloproteinases, key regulators of extra-cellular matrix activity, are known to contribute to atrial fibrosis and are upregulated during AF. Furthermore, overexpression of TGF- $\beta$ 1 can also cause selective atrial fibrosis and AF (17).

### ➤ Inflammation

There are a number of lines of evidence that point to a role for local inflammatory processes in the pathophysiology of AF. Firstly, markers of inflammation, such as C-reactive protein, IL-6, IL-8, IL-1 $\beta$ , and TNF- $\alpha$ , have been associated with the incidence, severity, and recurrence of AF. These markers are secreted by epicardial fat, and may have local pro-inflammatory effects on the adjacent atrial myocardium that facilitate arrhythmogenesis. Secondly, another study noted that epicardial fat had greater 18-fluorodeoxyglucose uptake on positron emission tomography when compared with subcutaneous or other visceral adipose tissue depots; these observations may be consistent with an inflammatory activity of epicardial fat that contributes to the development of AF (11).

Finally, systemic anti-inflammatory therapies such as corticosteroids appear to reduce atrial remodeling and AF incidence (18)

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