Atrial fibrillation (AF) is the most frequently observed arrhythmia in the clinic, affects 2 to 6 million people in the United States, and is known to increase the risk of stroke, heart failure, and sudden death. Epidemiological studies have identified multiple factors that enhance risk for susceptibility to AF, including age, coronary artery disease, heart failure, hypertension, and, more recently, obesity. The increase in the incidence of obesity is at alarming proportions; more than one third of the adult population in the United States is classified as obese, an observation that is expected to affect AF incidence. Several mechanisms have been proposed to underlie the observed association between obesity and AF, including increased left atrial dimensions, impaired diastolic function, and inflammatory processes, as well as enhanced fibrosis and fatty infiltration of the myocardium and associated comorbidities such as obstructive sleep apnea. All such events lead to electrophysiological and structural remodeling of the atrium and predispose to AF induction and maintenance.

In this brief viewpoint article, we will focus on the emerging evidence showing the importance of adipose tissue in increasing the risk of AF in obesity and outline possible molecular/ionic mechanism(s) involved.

**Myocardial Adipose Tissue and AF**

The fat in the atria is located either (1) on the outside of the visceral pericardium and on the external surface of the parietal pericardium (pericardial fat) or (2) between the myocardium and the visceral pericardium (epicardial fat). The embryonic origin of these fat depots and their composition is different in nature. Epicardial fat in particular has been the focus of adipose tissue studies in the atrium because of its contiguity with the myocardium and a shared vasculature (important for paracrine effects) and because it is a better predictor of paroxysmal AF. The authors speculated that EAT was involved in the establishment of (fibro) fatty infiltrates in the myocardium. In healthy lean individuals, EAT is ≈1% of the mass of the organ, a percentage that dramatically increases with obesity. An increase in EAT is expected to result in more extensive fatty infiltration in the myocardium. Moreover, presence of the ubiquitous

**EAT and Atrial Remodeling**

Several studies have provided evidence linking EAT to structural and electric remodeling of the myocardium, which have major implications on wave propagation. These studies, for example, have shown extensive atrial electric remodeling, including changes in effective refractory period (usually shortened) and alterations in impulse propagation (slowing), both of which allow for high-frequency rotors to sustain AF in both patients and animal models. One way to quantify rotors is to examine their rate of activation in the frequency domain and characterize the dominant frequency. Nagashima et al investigated the correlation between EAT and AF electric signals in patients with paroxysmal and persistent AF and found that high-dominant-frequency sites were located adjacent to EAT sites in the atrium; in contrast, there was poor correlation between complex fractionated electrograms and EAT locations. The authors speculated that EAT was involved in the establishment of high-dominant-frequency sites, either through locally released cytokines leading to inflammation or by modulating the function of ganglionic plexi in the fat depot, both ultimately affecting the atrial electric properties.

There is increasing interest to determine the precise origin of the (fibro) fatty infiltrates in the myocardium. In healthy lean individuals, EAT is ≈1% of the mass of the organ, a percentage that dramatically increases with obesity. An increase in EAT is expected to result in more extensive fatty infiltration in the myocardium. Moreover, presence of the ubiquitous

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**References**

1. The opinions expressed in this Viewpoint article are not necessarily those of the editors or of the American Heart Association.
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mesenchymal stromal cells, with a potential to undergo adipogenesis, also requires consideration because mesenchymal stromal cells have been reported to play a role in arrhythmogenic cardiomyopathy. The possibility exists, for example, that oxidative stress attendant to rapid electric pacing or to excess adiposity may enhance adipogenesis in such cells, thereby also contributing to myocardial adiposis. Recent studies have started to explore the mechanisms of electric remodeling because of EAT. In a sheep model of obesity obtained by high-calorie diet feeding, it was found that along with an increased epicardial fat infiltration in the left atrium, the conduction velocity was reduced, conduction heterogeneity was increased, and voltage heterogeneity was increased, but there was no change in the effective refractory period compared with controls. However, the underlying ionic mechanisms were not investigated. Because EAT is a source of free fatty acids, O’Connell et al investigated their effects on the sheep atrial electrophysiological properties. The results indicated that when sheep left atrial myocytes were incubated in stearic acid for 24 hours, the action potential duration was shortened and was attributable to reduced densities of both the L-type Ca²⁺ current and the Ca²⁺-independent transient outward K⁺ current, Iₒ. Furthermore, stearic acid was shown to disrupt the t-tubule structure. Those findings recapitulated in part the phenotype of atrial cells isolated from patients with persistent AF, although the precise relationship between how EAT secretes these free fatty acids in obesity and how that can lead to chronicity of AF remains unclear.

The sheep experimental model of obesity also showed an increase in interstitial fibrosis and enhanced levels of profibrotic transforming growth factor-β expression, along with infiltration of the left atrium by EAT. These structural modifications could have directly contributed to the reduced conduction velocities in the left atrium of obese sheep by creating barriers for impulse propagation. Moreover, recent studies have now actively begun to explore the link between EAT and fibrosis. Venteclé et al obtained samples of EAT from patients undergoing coronary bypass surgery and exposed an organo-culture model of adult rat atria to a conditioned medium of EAT-derived adipose tissue maintained in culture. The results indicated that when exposed to EAT-conditioned medium (but not subcutaneous adipose tissue), enhanced fibrosis was seen in the rat atrial organo-culture model (Figure 1A). Fibrosis induction was blocked when the secretion of adipofibroline, Activin A (a member of the transforming growth factor-β superfamily), was blocked with neutralizing antibodies. Human EAT releases cytokines such as matrix metalloproteinases, which may also contribute to extracellular matrix remodeling in the atrium. However, the possibility of other adipokines such as omentin being involved cannot be ruled out, because a recent genomic analyses found that 2728 genes are differentially upregulated in EAT versus subcutaneous fat, and many of these are related to extracellular matrix remodeling and inflammation. The properties of the EAT also seem to be nonstatic, that is, they change in response to rapid atrial pacing and AF. In a pig model of rapid atrial tachypacing, using microarrays and real-time quantitative polymerase chain reaction, it was found that atrial adipocyte/adipositas-related gene expression was substantially altered; however, how this could lead to either fat infiltration or fibrosis remained unclear. Further evidence of a close relationship between fat and fibrosis was obtained in a recent study that obtained atrial samples from patients who underwent cardiac surgery and from a sheep model of atrial tachypacing that induced persistent AF. The study showed an inverse correlation between fibrotic remodeling and amount of sub-EAT, suggesting conversion of adipose tissue to fibrotic tissue. A similar fibrofatty infiltration was seen in the sheep left atrium of persistent AF model. The subepicardial fat infiltrations were digitized and classified into 4 different grades, which are shown in Figure 1B and quantified in Figure 1C. Compared with healthy controls, AF caused a shift to higher grades of infiltration. It was suggested that an increase in cytotoxic T lymphocytes and adipocyte cell death might be involved in the observed fibrofatty accumulation. Thus, these emerging data point toward a close relationship between EAT and the formation of fibrotic tissue, which may accelerate progression to persistent AF.

Molecular/Ionic Mechanisms

The molecular mechanisms underlying EAT-induced electric and structural remodeling via paracrine signaling mechanisms are ill understood. There is increasing evidence implicating reactive oxygen species and Toll-like receptors (Figure 2). Reactive oxygen species are known to be upregulated in AF and may represent a possible link between cytokines/adipokines secreted by EAT and electrostructural remodeling. Reactive oxygen species is known to affect the electric properties of the atria by modulating ion channel properties either directly or indirectly and may also influence fibroblast proliferation. A recent study using human atrial tissue reported that EAT-secreted adipokine influenced myocardial nicotinamide adenine dinucleotide phosphate oxidase activity via endocrine or paracrine effects. Furthermore, this modulation was mutual, in that it was found that oxidation products (such as 4-hydroxynonenal) also regulated the expression of adiponectin in EAT. However, the role of other sources of reactive oxygen species that are important in AF perpetuation, for example, from mitochondria, and how these are related to adipokine production remain to be elucidated. It is now well understood that membrane ion channels, as well as intracellular Ca²⁺ homeostasis, are remodeled in both paroxysmal and persistent AF, and govern the electric properties of both atrial myocytes and fibroblasts and also cell proliferation in the latter. Similarly, there is evidence pointing to the presence of ion channels in the adipocytes as well. For example, voltage-gated K⁺ channels have been identified in isolated cultured brown fat cells from neonatal rats, and more recently, the transient receptor potential vanilloid 3 channel, TRPV3, has been shown to suppress adipocyte differentiation. However, the expression of such ion channels in EAT from the atrium, their similarity to ion channels found in

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<th>Nonstandard Abbreviations and Acronyms</th>
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atrial myocytes and fibroblasts, and finally their function and role in influencing atrial remodeling and susceptibility to AF remain unexplored.

Finally, from a variety of studies including observational, autopsy, in vivo and in vitro, it is abundantly clear that excess of EAT is associated with arrhythmogenesis. However,
many challenges preclude an adequate understanding of the precise mechanisms by which EAT enhances arrhythmogenicity. One significant challenge is the availability of imaging modalities and development of signal-processing techniques capable of adequately resolving details of EAT infiltrations in the myocardium. Data from the quantification of EAT will need to be correlated with optical mapping data on ex vivo intact hearts to fully appreciate the role of fatty infiltrations in wave dynamics. Moreover, a comparative biochemical analysis, including proteomics, of myocardial adipose tissue biofactors from normal weight and obese individuals must be conducted to understand underlying signaling mechanisms, as well as post-translational modifications, such as via O-GlcNAcylation. An overall schema of mechanisms underlying increased AF propensity in obesity is shown in Figure 2.

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References


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