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REVIEW

Role of Epicardial Adipose Tissue in Triggering and Maintaining Atrial Fibrillation

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Abstract

Atrial fibrillation is the most common arrhythmia leading to cardiogenic stroke. Without membranous sructure between epicardial adipose tissue and atrial myocardium, epicardial adipose tissue directly covers the surface of the atrial myocardium. The formation of an epicardial adipose tissue inflammatory microenvironment, fibrosis, infiltration by epicardial adipose tissue, autonomic dysfunction and oxidative stress are important mechanisms that trigger and maintain atrial fibrillation. Those mechanisms are reviewed herein.

Keywords: Atrial fibrillation; Epicardial adipose tissue; Macrophages; Adipocytes

Introduction

Atrial fibrillation (AF) is the most common arrhythmia leading to cardioembolic stroke. AF affects at least 60 million people worldwide, and substantially influences mortality and health care expenditures [1]. Many fibrosis-insulated atrial bundles are present in the left atrium. These fibrosis bundles contribute to the complex architecture of the atrium and cause significant differences between endocardial and epicardial action in patients with AF [2]. Obese people show greater conduction abnormalities and fractionation in local electrograms than non-obese people. The low voltage areas are mainly concentrated in the posterior and inferior left atrium, and cardiac magnetic resonance imaging shows more epicardial adipose tissue (EAT) distributed on the posterior and inferior left atrial surfaces [3]. EAT is an important adjacent tissue that is closely associated with the occurrence and development of AF, and is independently associated with AF recurrence after atrial fibrillation ablation [4]. EAT-based left atrium ablation has shown relatively high efficacy in treating persistent AF [5]. These findings indicate that EAT's triggering and maintaining AF may serve as a target for clinical treatment.

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EAT Histology and Physiology

EAT is a unique adipose tissue located between the visceral layer of the serous pericardium and the myocardium. Embryologically, EAT is derived from the splanchnopleuric mesoderm. EAT covers almost 80% of the surface area of the heart and accounts for 20% of the total heart weight [6]. Without connective tissue and fascial tissue, EAT directly attaches to the surface of the heart and surrounds the large coronary vessels. EAT is composed

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of many adipocytes, preadipocytes, fibroblasts, macrophages and lymphocytes [7].

EAT has high metabolic activity and is a unique adipose tissue [6]. In healthy people, EAT expresses high levels of uncoupling protein-1 (UCP-1), positive regulatory domain containing 16 and peroxisome proliferator-activated receptor gamma coactivator 1-α. UCP-1 uncouples mitochondrial respiration from ATP production, thus facilitating non-shivering thermogenesis, which is involved in thermoregulation. In the absence of aponeurotic or connective tissues between the EAT and the myocardium, EAT provides a rich local source of free fatty acids that support the high energy demands of nearby cardiomyocytes, thus providing cardiac energy storage [8]. EAT also secretes multiple cytokines (such as adiponectin) that limit myocardial inflammation and fibrosis. Furthermore, EAT mechanically supports the coronary arteries, thereby preventing the arterial torsion caused by arterial impulses and systole, and it protects the cardiac autonomic nerve and ganglion plexus.

EAT and AF

Pathophysiology of EAT

The EAT distribution is altered in AF and coronary artery disease [9]. A ventricular dominant distribution of EAT is primarily observed in coronary artery disease, whereas in AF, EAT is primarily located in the left superior pulmonary vein, left inferior pulmonary vein, right superior pulmonary vein, the top of left atrium and its anterior surface. The anterior descending branch and atrioventricular groove also have a small amount of EAT [10]. A study of EAT obtained from 41 patients with coronary artery disease and AF has demonstrated that the EAT in peri-atrial, periventricular or peri-coronary regions has specific transcriptomic signatures. The periventricular EAT transcriptome is associated with genes involved in inflammation and immunity processes, and genes encoding the A, B, C transporters functioning in cellular detoxification and intracellular lipid transport. In contrast, peri-coronary EAT gene expression includes the cell cycle and sphingolipid metabolism pathways. Peri-coronary EAT gene expression includes many pro-inflammatory factors (such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and omentin1. Peri-atrial EAT is associated with expression of genes implicated in oxidative phosphorylation, muscular contraction, inflammation and calcium signaling [11, 12]. EAT provides a local source of inflammatory cytokines [13].

EAT, Inflammation and AF

A broad range of metabolic disorders represented by obesity and diabetes are accompanied by an increased volume of adipose tissue. Aging, systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis, inflammatory bowel disease, chronic pulmonary inflammation and other systemic inflammatory diseases are characterized by a chronic low-grade pro-inflammatory state that results in increased adipose tissue volume [14, 15]. The adipocytes gradually develop hypertrophy. When adipose tissue expands beyond the perfusion area of the blood supply, small ischemic and hypoxic areas form. In the non-ischemic regions, adenine nucleic acid transposase stimulates mitochondrial respiration, thus increasing oxygen consumption. Both ischemic and non-ischemic areas contribute to a relatively hypoxic environment in adipose tissue; consequently, adipocytes produce more hypoxia inducible factor-1α (HIF-1α) [16]. With the activation of the adipose tissue fibrotic transcription program induced by HIF-1α, expression of type I, type III and type IV collagen and lysine oxidase increases. Lysine oxidase cross-links type I and type III collagen, thus forming fibrillar collagen and promoting fibrosis. With adipocyte hypertrophy and increased fibrosis, adipocytes are surrounded by a tight fibrotic shell. Fibrosis interferes with the expansion of adipocytes, thus causing adipose cell injury and cell death. Subsequently, macrophage infiltration, macrophage activation, release of pro-inflammatory cytokines and inflammation result [17].

Cytokines (such as HIF-1α, monocyte chemoattractant protein-1, galectin-3 and leptin) secreted by dysfunctional adipocytes promote the local proliferation and recruitment of macrophages [17]. Vascular cell adhesion factor-1 expressed by adipocytes and α integrin dependent adhesion expressed by macrophages promote the retention

of macrophages in adipose tissue [18]. Adipocytes release exosomesized, lipid-filled vesicles, which serve as a source of lipids for local macrophages. These vesicles can modulate tissue macrophage differentiation and function by activating specific transcriptional profile [19]. Activated macrophages generate many inflammatory mediators (such as TNF-α, IL-6 and interleukin-1β (IL-1β) and monocyte chemoattractor protein-1). Those inflammatory factors induce macrophages to undergo pro-inflammatory polarization. TNF-α secreted by macrophages also enhances the expression of vascular cell adhesion factor-1 in adipocytes, which maintains the adhesion between macrophages and adipocytes [18]. Moreover, TNF-α directly promotes the release of adipocyte-free fatty acids. Toll-like receptor 4 (TLR4) is widely expressed on the surfaces of macrophages and adipocytes. Free fatty acids directly bind TLR4 and activate the pro-inflammatory nuclear transcription factor-κB signaling pathway in macrophages and adipocytes [20]. HIF-1α also induces macrophage pro-inflammatory polarization by regulating pyruvate dehydrogenase kinase 4, a key protein in glucose metabolism [21]. In addition. small lymphoid aggregates have been observed in EAT. Many activated $CD8^+$ T lymphocytes are present in the transition zone between adipocytes and fibrosis in the atrium [22]. Interferon-γ, which is secreted by lymphocytes, is important in the formation of an inflammatory environment [23].

EAT is an active endocrine organ. In the absence of aponeurotic or connective tissues between the EAT and the myocardium, hypertrophic adipocytes and activated immune cells secrete inflammatory factors (such as IL-1β, IL-6, interleukin-8 and TNF-α), which act on the adjacent atrium and mediate atrium remodeling. NOD-like receptor family protein-3 (NLRP3) inflammasome activity has been found in the atrial cardiomyocytes of patients with paroxysmal AF [24]. TNF-α activates caspase-1 expression and induces the activation of NLRP3. IL-1β also enhances the NLRP3 inflammasome signaling pathway, promotes the release of Ca^{2+} in the sarcoplasmic reticulum of cardiomyocytes and causes changes in action potential duration. The released Ca^{2+} increases AF susceptibility through activation of the Ca^{2+}/CaMK II/NLRP3 inflammasome signaling pathway [25]. In addition to promoting Ca^{2+}-handling abnormalities, inflammatory factors promote adjacent atrial fibrosis and electrical remodeling. C reactive protein damages the myocardium by activating the complement system and binding phosphatidylcholine, thus inhibiting Na^+/Ca^{2+} exchange in sarcolemmal vesicles. Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been demonstrated to have adverse effects on the cardiovascular system through several pathways. PCSK9 is a novel adipokine secreted by EAT, which promotes inflammation [26]. PCSK9 monoclonal antibody therapy has benefits in patients with AF and significantly decreases the incidence of AF events [27]. IL-1β and TNF-α are positively correlated with extracellular matrix volume in atrial tissue in patients with AF. Inflammation also modulates connexins associated with triggers and heterogeneous atrial conduction. Specific lateralization of Connexin40 and downregulation of Connexin43 decrease cardiomyocyte conduction velocity and promote the maintenance of AF [28]. In conclusion, inflammatory factors from EAT directly promote inflammation in adjacent atrial tissue and AF occurrence and development.

EAT Promotes Adjacent Atrial Fibrosis

Fibrosis is central to the pathophysiology of atrial fibrillation. A variety of cytokines (matrix metalloproteinases 2, matrix metalloproteinases 2 and activin A) released by EAT directly promote epicardial fibrosis and loss of epicardium continuity. With atrial fibrosis, transverse electrical conduction is impaired, electrical coupling between the epicardium and endocardium is interrupted, and electrical synchronization effects are decreased. Simultaneously, fibrosis increases the transmural conduction of the epicardium thus leading to changes in electrical activity [29]. The degree of atrial wall fibrosis influences the position of the AF rotor in the atria. The reentrant drivers of AF persistence may exist between fibrotic and non-fibrotic tissue [30]. The left atrium grows larger as the structure changes, thus making the rotor less likely to collide with the anatomical boundary. As a result, the rotor maintains its stability, and AF continues to occur.

Recent research has linked adiponectin, angiopoietin-like protein 2 (Angptl2), YKL-40 mRNA,

connective tissue growth factor and leptin with the triggering and maintenance of AF. Adiponectin, which is controlled by the serotonin receptor cascade, is an important hormone that decreases myocardial inflammation and fibrosis. It has a protective effect on the maintenance of postoperative sinus rhythm. With increasing serotonin receptor expression in hypertrophic adipocytes, adiponectin secretion decreases. Consequently, the protective effect of the heart is weakened, thereby providing a favorable environment for AF [31]. Angptl2 is a helical and fibrillin-like domain protein secreted by EAT. In fibroblasts cultured with Angptl2, the expression of α-smooth muscle actin, transcriptional growth factor-β1 and phosphorylated p38 mitogen-activated protein kinase is elevated. EAT-conditioned medium containing Angptl2 has been found to result in fibrosis on the atrial surface. These findings indicate that Angptl2 plays an important role in atrial fibrosis caused by paracrine of EAT [32]. YKL-40 mRNA is a new marker of cardiovascular disease that is highly expressed in the EAT of patients with AF. Its level shows a linear relationship with the expression of type I collagen in the atrium [33]. Connective tissue growth factor is closely associated with atrial diameter enlargement, myocardial fibrosis and atrial anatomical remodeling, and is an independent risk factor for AF [34]. Leptin directly regulates the expression of aldosterone synthase in adrenalcortical cells. Aldosterone synthase affects the secretion of aldosterone, which regulates myocardial fibrosis [35].

Extracellular vesicles (EVs) are membrane-bound organelles that transport proteins, nucleic acids and lipids to local or distant targets, and perform biological functions. Epicardial fat (eFat) derived EVs play a role in the pathogenesis of AF. EFat EVs from patients with AF contain high concentrations of pro-inflammatory cytokines, such as TNF-α and IL-6, and profibrotic cytokines such as osteopontin and the protective adipokine adiponectin [36, 37]. Shaihov-Teper et al. have injected eFat EVs from people with or without AF into the left ventricular free wall in Sprague-Dawley female rats. The rats' hearts treated with eFat EVs from people with AF showed extensive myocardial fibrosis, according to picrosirius red staining. Angiogenic tube formation assays of human umbilical vein endothelial cells incubated for 11 hours with eFat EVs from people with or without AF have indicated that endothelial cells take up eFat EVs, and that eFat EVs from people with AF have greater angiogenic effects than those from people without AF. The authors then generated sheets of hiPSC-derived cardiac cells expressing the genetically encoded voltage fluorescent indicator ArcLight to study the potential effects of eFat EVs on the electrophysiological properties of human cardiac tissue. Activation maps derived after programmed electric stimulation indicated sustained rotor activity after treatment with eFat EVs from patients with AF. EVs secreted from eFat carry pro-inflammatory, profibrotic and proarrhythmic molecules causing cellular, molecular and electrophysiological remodeling, thus resulting in atrial myopathy and the generation of an arrhythmogenic substrate for the initiation and maintenance of AF [38].

EAT Directly Infiltrates Atrial Tissue

In addition to their effects on inflammation and fibrosis, EAT adipocytes directly infiltrate into the myocardium in another potential mechanism of AF generation. Nalliah et al. have used oil-red-O staining to show the presence of cardiac adipose tissue on the epicardium. High resolution microscopic examination has revealed a heterogeneous interface between EAT and the epicardium, with irregular infiltration of adipose tissue. The area containing a cardiomyocytes and adipocytes showed the strongest conduction inhibition. A physical barrier formed by EAT directly infiltrated the myocardium, thus directly leading to a loss of connection between cardiomyocytes, resulting in uneven atrial voltage and abnormal conduction, and increasing AF susceptibility [36]. Suffee et al. have discovered that a group of cells originating from the epicardium may regulate the adipose-fibrosis balance. Subsets of adult epicardial-derived cells can be preprogrammed to differentiate into adipocytes or myofibroblasts, and contribute to adipose tissue infiltration of the subepicardium of atrium. In summary, physical conduction blocks from infiltrating adipocytes can cause atrial electrical conduction dysfunction [37].

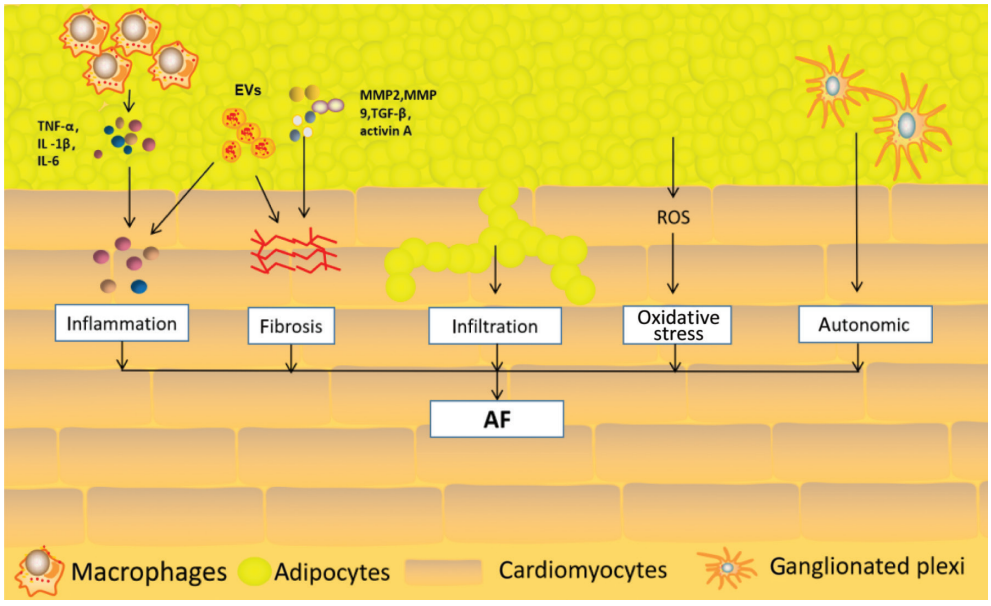

Figure 1 The Mechanism Through which EAT Triggers and Maintains Atrial Fibrillation.

Autonomic Dysfunction

The regulation of the autonomic nervous system plays a key role in the occurrence and maintenance of AF. The major anatomical ganglionated plexi are located mainly on left atrium EAT. EAT may have a triggering effect at the pulmonary veins. Increased EAT volume may alter the function of ganglionated plexi [39]. Activation of the ganglionated plexus within the EAT stimulates the autonomic nervous system, thus decreasing action potential duration and transiently increasing myocardial calcium [40].

Oxidative Stress

Oxidative stress is a pathophysiological mechanism of AF. EAT is a source of ROS. In a canine model of pacing AF, ROS in EAT have been found to be significantly elevated [41]. ROS can lead to endothelial cell damage and endothelial dysfunction, activate NADPH oxidase, and cause lipid peroxidation and intracellular Ca^{2+} overload [42]. ROS also stimulate mitogen-activated protein kinases 98 and the NLRP3 inflammasome, thus resulting in tissue fibrosis [43]. In rats with myocardial infarction, EAT reinforces cardiac fibroblast differentiation into myofibroblasts by elevating intracellular ROS levels [44]. These findings suggest that oxidative stress is a mechanism triggering AF.

Summary and Outlook

The formation of an EAT inflammatory microenvironment, fibrosis, infiltration of atrial tissue, autonomic dysfunction and oxidative stress are important mechanisms that trigger and maintain AF (Figure 1). Decreasing EAT inflammation can help patients with AF recover sinus rhythm [43]. Targeting EAT; integrating cutting-edge advances in new science, engineering and medicine efforts; and developing new theories, technologies and methods for AF treatment should be worthwhile future pursuits [45–48].

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Conflicts of interest

The authors declare they have no conflicts of interest.

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