Review

Understanding the Impact of Left Atrial Epicardial Adipose Tissue Thickness on Atrial Fibrillation: A Literature Review

Behzad Fahimi * and Somayeh Beikmohammadi *

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Understanding the Impact of Left Atrial Epicardial Adipose Tissue Thickness on Atrial Fibrillation: A Literature Review

Behzad Fahimi [1] and Somayeh Beikmohammadi [2]

[1] Academic Heart Center Duisburg, Duisburg, Nordrhein Westfallen, Germany
[2] Academic Hospital Elisabeth-Krankenhaus , Essen, Nordrhein Westfallen, Germany
* Correspondence: behzadfahimi@gmail.com (B.F.); soman10620@gmail.com (S.B.)

Abstract: Atrial fibrillation (AF) is a common cardiac arrhythmia associated with significant morbidity and mortality. The role of epicardial adipose tissue (EAT), particularly in the left atrium, has garnered attention in the pathophysiology of AF. This review aims to provide an overview of the association between the thickness of left atrial epicardial adipose tissue (LA-EAT) and the incidence of AF, while exploring the arrhythmogenic effects of LA-EAT and the impact of epicardial fat tissue changes with age and in pathological conditions. A comprehensive search of PubMed was conducted, and relevant studies were selected based on their inclusion criteria. The findings suggest that increased LA-EAT thickness is associated with an elevated risk of AF, potentially mediated through inflammatory and proarrhythmic effects. Age-related changes in epicardial fat tissue and alterations in pathological conditions, such as obesity, metabolic syndrome, and cardiovascular diseases, further contribute to the development and progression of AF. Further research is needed to deepen our understanding of these mechanisms and their clinical implications.

Keywords: epicardial adipose tissue; atrial fibrillation; inflammation; cardiac arrhythmia; left atrium

Introduction

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia characterized by rapid and irregular electrical activity within the atria, leading to impaired cardiac function and an increased risk of stroke and heart failure. The pathophysiology of AF involves complex interactions between structural, electrical, and autonomic remodeling processes. Recent investigations have highlighted the potential role of epicardial adipose tissue (EAT), specifically in the left atrium, in the initiation and perpetuation of AF (1,2). The relevance between the thickness of left atrial epicardial adipose tissue (LA-EAT) and the incidence of AF has been evaluated in several studies. LA-EAT has been found to be associated with AFACS, and its measurement has been shown to be independent of the methods used [3,4]. Inflammation and adipose tissue density in the LA have also been found to be related to AF, providing incremental value over other variables associated with AF (2). Epicardial fat, including EAT, has been implicated in the electrical, structural, and molecular mechanisms of AF initiation and maintenance (5). Furthermore, obesity, including excessive visceral adiposity, has been shown to have chamber-specific effects on the heart, with greater EAT being associated with worse atrial function and an increased risk of AF (3). These findings suggest that LA-EAT and epicardial fat tissue changes play a role in the arrhythmogenic effects of AF and may serve as potential markers and therapeutic targets for AFACS.

Methodology

A systematic search was performed on PubMed, Google Scholar, Web of Science and Scopus using relevant keywords, such as "atrial fibrillation," "left atrial epicardial adipose tissue," "echocardiography," "adiposity," "arrhythmogenesis," "epicardial fat tissue," "age," "obesity," "metabolic syndrome," and "cardiovascular diseases" (6,7,8). Only studies published in English and

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conducted on human subjects were included. The search was limited to articles published up to September 2022. The initial search identified a total of 78 studies.

Role of Epicardial Adipose Tissue in Cardiac Physiology and Pathology

Epicardial adipose tissue plays a multifaceted role in cardiac physiology and pathology. While it exerts cardioprotective effects through paracrine signaling and thermoregulation, pathological changes in EAT can lead to a pro-inflammatory state with detrimental implications for the heart

Paracrine Signaling and Cardioprotection:

Adipose endothelial tissue (EAT) releases a variety of bioactive compounds, such as adipokines, cytokines, and growth factors. These molecules have a paracrine effect on the surrounding myocardium. (9). Some of these factors, such as adiponectin and omentin, have anti-inflammatory and insulin-sensitizing properties and contribute to cardioprotective effects (10). Adiponectin, in particular, has been associated with reducing and ameliorating myocardial inflammation endothelial function (11).

Thermoregulatory Role:

function (12, 13, 14). serves as thermogenic source to combat hypothermia and protect the myocardium from temperature variations (15). In addition, EAT facilitates the transport of fatty acids to the myocardium and adapts its metabolic activity to the prevailing conditions and acts as a brown or beige grease reservoir as needed. EAT also expresses genes and secretes cytokines involved in it thermogenesis and regulation of lipid and glucose metabolism of the adjacent myocardium (16). In addition, EAT shares its blood supply with the coronary arteries and provides physical protection. to the heart.The current results underscore the crucial role of EAT in maintaining the stability of °C raises myocardial temperature and facilitates optimal heart function(17).

Mechanical Cushioning:

Epicardial adipose tissue (EAT) plays a significant role as a mechanical cushion that safeguards the heart from external impacts and provides support during cardiac contractions. This protective mechanism is evidenced by studies (14, 12, 18) that have shown EAT to act as a buffer, absorbing fatty acids and safeguarding the heart against high levels of fatty acids (19). Furthermore, EAT functions as a protective pad, shielding the coronary arteries' abnormal curvature. Additionally, EAT may contribute to buffering the coronary arteries against torsion induced by the arterial pulse wave and cardiac contraction. The close anatomical proximity of EAT to the heart allows it to have a direct impact on cardiac function (20).

Pathological Implications of EAT:

Inflammation and Fibrosis:

Under pathological circumstances, such as obesity, epicardial adipose tissue (EAT) experiences hypertrophy, resulting in dysfunctional behavior that alters the secretion of adipokines and pro-inflammatory cytokines (21). This state of chronic inflammation is a significant contributor to the emergence of myocardial fibrosis, which further promotes adverse cardiac remodeling (22).

Coronary Artery Disease (CAD):

EAT has been implicated in the pathogenesis of CAD. Increased EAT volume has been associated with atherosclerosis, possibly due to the release of pro-atherogenic factors that promote vascular inflammation and endothelial dysfunction (23).

Arrhythmogenesis:

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Recent findings indicate that epicardial adipose tissue (EAT) may contribute to arrhythmogenesis, affecting cardiac electrophysiology and conduction, and thereby promoting the onset of atrial fibrillation and ventricular arrhythmias (20). Numerous studies have demonstrated that EAT exhibits an inflammatory profile, characterized by the release of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin 1 beta (IL1B), and interferon-alpha 2 (IFNA2) (24). Additionally, investigations have shown that EAT has a discernible impact on cardiovascular haemodynamics and metabolic profile in heart failure patients, with elevated EAT levels associated with inferior haemodynamic and metabolic profiles (25). Moreover, EAT has been found to affect cardiac function, with changes in EAT thickness linked to left ventricular systolic dysfunction (26). Therefore, these observations suggest that EAT may indeed be a contributing factor in the development of arrhythmogenesis.

Cardiac Adiposity-Related Cardiomyopathy (CARC):

The excessive expansion of epicardial adipose tissue (EAT) has been associated with the development of cardiac adiposity-related cardiomyopathy (CARC). CARC is characterized by diastolic dysfunction and impaired myocardial compliance, as evidenced by various studies (27,28). It is worth noting that obesity cardiomyopathy represents a unique disease entity that develops independently of comorbidities such as hypertension and coronary artery disease. This disease is characterized by alterations in adipose tissue function, inflammation, and metabolism (29). Studies have linked obesity-related cardiomyopathy to changes in substrate utilization, tissue metabolism, oxidative stress, and inflammation, which eventually lead to myocardial fibrosis and cardiac dysfunction(30). Additionally, obesity is an independent risk factor for the development of left ventricular hypertrophy (LVH) and heart failure (HF), particularly HF with preserved ejection fraction (31). These findings suggest that excessive expansion of EAT and obesity-related metabolic traits contribute to the development of CARC, leading to diastolic dysfunction and impaired myocardial compliance.

Epicardial Fat Tissue Changes with Age and in Pathological Conditions:

1. Age-Related Changes:

With the progression of time, discernible modifications occur in the epicardial adipose tissue. These alterations encompass an upsurge in the volume of epicardial adipose tissue and changes in the size and morphology of adipocytes (32). Age-related metabolic adjustments, namely insulin resistance and modified lipid metabolism, can contribute to the expansion of epicardial adipose tissue (33). These shifts may impel a pro-inflammatory state within the adipose tissue, which could lead to the release of inflammatory mediators and an increased susceptibility to cardiovascular diseases, including atrial fibrillation (34).

2. Obesity:

Excessive adiposity, especially visceral adipose tissue, can lead to an expansion of epicardial fat (35,32). In obese individuals, epicardial fat tissue may exhibit signs of dysfunction, characterized by altered adipokine secretion, increased oxidative stress, and enhanced inflammatory responses (36). These pathological changes contribute to the development of a pro-inflammatory milieu that promotes cardiac remodeling and increases the susceptibility to atrial fibrillation (37).

3. Metabolic Syndrome and Insulin Resistance:

Metabolic syndrome, a cluster of conditions including central obesity, hypertension, dyslipidemia, and insulin resistance, is closely associated with epicardial fat alterations(38). Insulin resistance is indeed a crucial factor in promoting epicardial fat deposition and inflammation, which are closely associated with metabolic syndrome. Studies have shown that both metabolic syndrome and insulin resistance are related to alterations in epicardial fat. In particular, insulin resistance has been found to be associated with increased adipose tissue insulin resistance index (Adipo-IR) and higher levels of epicardial fat(39).

4. Cardiovascular Diseases:

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Various cardiovascular diseases, including coronary artery disease, heart failure, and hypertension, can impact epicardial fat tissue. These conditions are often characterized by chronic inflammation and increased oxidative stress. Studies have shown that increased epicardial fat thickness (EFT) is associated with the exacerbation of pathological mechanisms involving oxidative stress and inflammation within the heart, which may accelerate the development of cardiovascular diseases (CVDs) (40). Echocardiographic epicardial adipose tissue (EAT) has been found to be inversely correlated with natriuretic peptides and C-reactive protein in heart failure patients with reduced ejection fraction (HFrEF), although there is a direct association with these markers in heart failure patients with preserved ejection fraction (HFpEF) (26). In patients with coronary artery disease (CAD), inflammation of the epicardial adipose tissue (EAT) has been found to be significantly increased, suggesting a significant relationship between EAT inflammation and CAD pathogenesis (32).

Association between LA-EAT Thickness and Incidence of Atrial Fibrillation

1. Imaging Techniques for LA-EAT Assessment:

The evaluation of the thickness of left atrial epicardial adipose tissue (LA-EAT) and its correlation with the incidence of atrial fibrillation (AF) has been the subject of investigation utilizing diverse non-invasive imaging modalities. A particular study revealed that LA-EAT volume and thickness were notably elevated in individuals with AF following cardiac surgery, thus signifying a relationship between EAT and AFACS (41). Another study demonstrated that quantification of LA fibrosis by means of cardiac MRI was linked to a heightened risk of AF recurrence subsequent to AF ablation, while augmented LA volume was linked to AF recurrence to a lesser extent (43). Moreover, the ratio of central to marginal adipocyte diameter in EAT was established to be associated with fibrotic remodeling of EAT, and the percent change in EAT fat attenuation measured via CT imaging was able to detect this remodeling noninvasively (44). Thus, both echocardiography and cardiac MRI have been employed to gauge LA-EAT thickness and offer insights into its link with AF incidence (45,46).

2. Observational Studies on LA-EAT Thickness and AF Incidence:

The augmentation of left atrial epicardial adipose tissue (LA-EAT) thickness is positively correlated with an augmented susceptibility to the development of atrial fibrillation (AF) (47, 48). In patients with AF, the thickness of LA-EAT has been discovered to be significantly higher in comparison to individuals without AF (49). Furthermore, the thickness of LA-EAT has been demonstrated to be a predictor of the emergence of new-onset AF in different clinical contexts (50). The thickness of LA-EAT has also been linked with diminished left atrial appendage (LAA) emptying flow velocity, thereby increasing the likelihood of thromboembolic phenomena in the presence of AF (51). These observations propose that augmented thickness of LA-EAT may play a contributory role in the development and severity of AF.

3. Meta-analyses and Systematic Reviews on LA-EAT Thickness and AF Risk:

Meta-analyses and systematic reviews have confirmed that elevated epicardial adipose tissue (EAT) thickness is significantly associated with an increased risk of atrial fibrillation (AF) incidence(52). These comprehensive analyses have provided a more robust assessment of the association between EAT thickness and AF risk by combining data from multiple studies (53). They have also underscored the potential clinical implications of EAT assessment as a predictive tool for AF risk stratification(54,3)

Impact of LA-EAT Thickness on AF Outcomes and Recurrence:

Increased thickness of epicardial adipose tissue in the left atrium (LA-EAT) has been linked to a greater likelihood of recurrence of atrial fibrillation (AF) following catheter ablation (55). In addition, LA-EAT thickness has been examined in relation to the progression of AF, response to treatment, and recurrence rates (56). LA-EAT serves as a potential predictor of adverse outcomes and recurrence in AF patients (3). Moreover, individuals with thicker epicardial adipose tissue (EAT) have exhibited

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an inferior response to antiarrhythmic therapy (57). The research revealed that EAT thickness and left atrial volume index (LAVI) were independent predictors of prolonged atrial electromechanical delay (AEMD), and both were closely associated (58). This may account for the poorer response to antiarrhythmic therapy seen in patients with thicker EAT.

The potential mechanisms linking Epicardial Adipose Tissue to atrial fibrillation

Epicardial adipose tissue (EAT) is a tissue which is metabolically active, and it secretes a diverse range of bioactive molecules including pro-inflammatory cytokines, adipokines, chemokines and growth factors. The presence of excessive EAT adjacent to the heart can lead to a paracrine effect on adjacent cardiac tissue, particularly the atrial tissue. Research data indicate that systemic inflammation can result in rapid electrical remodeling of the atria, which is achieved through the upregulation of interleukin-6 and downregulation of cardiac connexins. During the occurrence of active inflammatory processes, this can lead to an increase in the risk of atrial fibrillation and its associated complications.

Electrical Remodeling:

Inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) can disrupt normal ion channel function, leading to alterations in atrial conduction and repolarization. These changes create an arrhythmogenic substrate that facilitates the initiation and perpetuation of AF(61,62)

Structural Remodeling: EAT-derived inflammatory mediators can induce fibrosis and hypertrophy in the atrial tissue (63). This fibrotic remodeling results in the formation of fibrotic patches and alterations in the extracellular matrix, providing a substrate for the maintenance of reentrant circuits, a common mechanism in AF(64).

Impact of EAT on the Autonomic Nervous System and its Influence on Atrial Electrophysiology:

The autonomic nervous system plays a crucial role in regulating cardiac electrophysiology, and EAT has been shown to interact with the autonomic nervous system, further influencing AF development(65,18)

Neural Cross-Talk: EAT is in close proximity to the cardiac sympathetic and parasympathetic ganglia(66). The release of adipokines from EAT can influence the activity of these cardiac autonomic ganglia, leading to an imbalance in sympathetic and parasympathetic tone. Sympathetic dominance can increase atrial excitability and predispose the atria to arrhythmias, including AF(67).

Adrenergic Stimulation: EAT-derived norepinephrine and other adrenergic substances can directly affect atrial ion channel function and electrical properties, leading to pro-arrhythmic effects(68).

Vagal Modulation: Parasympathetic stimulation can promote bradycardia and trigger AF episodes in certain situations, and EAT may contribute to increased vagal tone in the atria(67,68)

Overall, the combination of EAT-derived inflammatory mediators and their influence on the autonomic nervous system creates a favorable environment for the initiation and perpetuation of AF(25). The interplay between inflammation, structural changes, and autonomic imbalance contributes to the pathophysiology of AF, making EAT an important factor in AF development.

Understanding these potential mechanisms is crucial for developing targeted therapeutic strategies to prevent or treat AF.

Therapeutic Implications and Effect of Cardiometabolic Drugs on Epicardial Fat Tissue:

Epicardial adipose tissue (EAT) has become a significant contributor to cardiovascular and metabolic disorders and has attracted great interest in research into its therapeutic implications.

Statin Therapy and EAT:

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The efficacy of statins in reducing EAT thickness was demonstrated in the study by Nakazato et al. (9) Statin therapy may lead to a reduction in EAT volume, potentially contributing to improved cardiovascular outcomes. The correlation between statin use and changes in coronary artery plaque composition further supports the potential benefits of statins in cardiovascular health.

Impact of XBP1 Splicing and EAT Regulation:

In the study by Ye et al. (27), Sustained activation of the XBP1 splice has been associated with endothelial apoptosis and the development of atherosclerosis in response to impaired perfusion. This highlights the importance of understanding the molecular pathways involved in EAT regulation and the potential impact of cardiometabolic drugs on these pathways.

Thiazolidinediones (TZDs) and EAT Modulation:

TZDs, such as pioglitazone, have been investigated for their effects on EAT. Dutour et al. (28) reported that TZDs exhibit insulin-sensitizing and anti-inflammatory properties, leading to reduced EAT volume and improved cardiometabolic risk factors. These findings suggest the therapeutic potential of TZDs in EAT modulation and their role in cardiovascular risk reduction.

Bariatric Surgery and EAT Reduction:

Bariatric surgery, as studied by van den Heuvel et al. (29), has shown significant reductions in EAT volume in the context of obesity-related EAT expansion. This underscores the effectiveness of surgical interventions in targeting excess EAT in severely obese individuals.

Lifestyle Modifications and EAT:

Additionally, lifestyle modifications, including dietary interventions and increased physical activity, have demonstrated promise in reducing EAT volume and improving cardiovascular risk factors (70, 30).

Inflammation and EAT:

Chronic inflammation within EAT contributes to adverse cardiac remodeling and cardiovascular diseases. Zuriaga et al. (71) explored the activation of non-canonical WNT signaling in human visceral adipose tissue, which contributes to local and systemic inflammation. This emphasizes the potential of anti-inflammatory agents, such as colchicine and methotrexate, in reducing inflammatory markers within EAT (72).

Novel Therapeutic Targets for EAT Modulation:

Novel therapeutic targets for EAT modulation are also being explored. Van den Heuvel et al. (29) investigated the effects of blocking the renin-angiotensin-aldosterone system (RAAS) with angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) in a mouse model of obesity-related cardiomyopathy. They reported favorable effects on EAT volume and function, potentially through reduced inflammation and fibrosis.

Meta-analysis and Efficacy of Cardiometabolic Drugs on EAT:

A recent systematic review and meta-analysis by Karampetsou et al. (72) evaluated the efficacy of cardiometabolic drugs in reducing EAT thickness. The findings from this meta-analysis further support the potential of pharmacological interventions for targeting EAT and reducing cardiovascular risk.

Limitations and Future Directions:

Standardization of LA-EAT Measurement:

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One of the primary predicaments in evaluating the thickness of LA-EAT is the absence of uniform measurement protocols. Varied imaging strategies and analytical methods have been implemented in different investigations, thereby inducing irregularities in LA-EAT measurements (73). It is indispensable to undertake endeavors aimed at instituting a standardized and replicable mode of LA-EAT assessment, thereby enabling more dependable comparisons between studies and promoting the assimilation of LA-EAT data into clinical practice.

6.2. Longitudinal Studies and Prospective Trials:

Although observational studies have provided valuable insights into the association between LA-EAT thickness and AF incidence, they inherently carry limitations, such as potential confounding factors and reverse causality (73,74). Longitudinal studies and well-designed prospective trials are necessary to establish a cause-and-effect relationship between LA-EAT thickness and AF development (75). These studies can help identify the temporal sequence of events and clarify whether increased LA-EAT thickness is a predictor or a consequence of atrial fibrillation.

6.3. Integration of LA-EAT Thickness with Existing AF Risk Scores:

Current risk stratification tools for atrial fibrillation (AF) primarily focus on clinical factors and traditional biomarkers. However, the incorporation of left atrial epicardial adipose tissue (LA-EAT) thickness into existing risk scores could improve their predictive value and refine patient-specific risk assessment. By considering LA-EAT as an additional imaging biomarker, clinicians may enhance their ability to identify individuals at higher risk of developing AF and implement preventive strategies accordingly(75,76)

Conclusion:

The association between LA-EAT thickness and atrial fibrillation has emerged as a promising area of research with potential clinical implications. Studies have demonstrated a significant link between increased LA-EAT thickness and AF incidence. However, several limitations and challenges need to be addressed to fully utilize LA-EAT assessment in clinical practice. Standardization of measurement techniques, longitudinal studies, and the integration of LA-EAT data into existing risk scores are essential steps in advancing our understanding of LA-EAT's role in atrial fibrillation. As this field continues to evolve, further research is warranted to determine the precise mechanisms underlying the association and to explore the potential of LA-EAT as a therapeutic target in atrial fibrillation management.

In summary, LA-EAT thickness is closely associated with the pathogenesis of atrial fibrillation through various underlying mechanisms. Inflammation, fibrosis, disrupted electrophysiology, and mechanical effects contribute to the pro-arrhythmogenic environment. Clinical applications of LA-EAT thickness measurement include risk stratification, predictive value assessment, therapeutic targeting, and guiding treatment strategies in AF management.

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