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Epicardial Fat, Paracrine-mediated Inflammation and Atrial Fibrillation

Nora Rat[1,2], Adriana Mitre[1], Szilamér Korodi[1,2], István Benedek Jr[1,3], Erzsébet Lázár[1,3], Johanna Kéri[1,3], Annamária Pakucs[1,3], István Benedek[1,3]

[1] University of Medicine and Pharmacy, Tîrgu Mureș, Romania
[2] Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Tîrgu Mureș, Romania
[3] Clinic of Hematology and Bone Marrow Transplantation Unit, Tîrgu Mureș, Romania

CORRESPONDENCE

Adriana Mitre
Str. Gheorghe Marinescu nr. 38
540139 Tîrgu Mureș, Romania
Tel: +40 265 215 551
E-mail: adimitre@yahoo.com

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Nora Rat • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: ratnora@gmail.com

Szilamér Korodi • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: szilamerkorodi@yahoo.com.

István Benedek Jr • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: benedekistvan73@yahoo.com

Erzsébet Lázár • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: erzsebetlazarbenedek@gmail.com

Johanna Kéri • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: johannakeri@gmail.com

Annamária Pakucs • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: pakucs.annamaria@gmail.com

István Benedek • Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: istvan.benedek@umftgm.ro

ABSTRACT

Atrial fibrillation is the most frequent arrhythmia in adults, becoming more frequent with age. Recent clinical studies demonstrated that epicardial fat is linked with atrial fibrillation induction and recurrence. The arrhythmogenic mechanism consists in the fact that the epicardial adipose tissue is metabolically active, inducing local inflammation and enhancing the oxidative stress, which lead to atrial fibrillation as well as atherosclerosis. Having metabolic activity and secreting various anti- and pro-inflammatory biomarkers, the fat surrounding the heart has been linked to the complex process of coronary plaque vulnerabilization. This clinical update aims to summarize the role of epicardial adipose tissue in the pathogenesis, persistence, and severity of atrial fibrillation.

Keywords: atrial fibrillation, pericardial fat, inflammation, noninvasive cardiac imaging

INTRODUCTION

Atrial fibrillation (AF) is the most frequent rhythm disturbance, its incidence being higher with increasing age.[1] It has been estimated that AF will affect around 18 million people in Europe by 2060.[2] There are a series of risk factors that can lead to development of AF including old age, level of physical activity, smoking, diabetes mellitus, arterial hypertension, heart failure, coronary heart disease, obstructive sleep apnea, and obesity. Both increased body mass index and epicardial fat volume have been associated with the risk of AF.[3–6]

Several studies have researched the association of epicardial adipose tissue (EAT) and the burden of coronary atherosclerosis.[7,8] EAT presents various roles, including thermoregulation and mechanical protection of the heart's vascularization and innervation. On the other hand, having metabolic activity and secreting various anti- and pro-inflammatory biomarkers, the fat surrounding the heart has been linked to the destabilization process of coronary plaques.[9,10] Furthermore, subjects with increased epicardial fat thickness or volume have

an increased risk of major adverse cardiac events, as well as a higher risk for multi-vessel coronary artery disease, presenting also an increased calcium score, which is an established marker for the severity of coronary artery disease.[11–14] This clinical update aims to summarize the role of EAT in the pathogenesis, persistence, and severity of atrial fibrillation.

EPICARDIAL FAT, ATRIAL REMODELING AND ARRHYTHMOGENESIS

A series of studies have confirmed the association of EAT with the presence of AF.[15] There are no intervening structures between EAT and the myocardium. EAT is overlying the right ventricle, coronary arteries, left ventricle apex, and the atria.[16] EAT is a metabolically active tissue, and it has paracrine effects on the atrial myocardium by secreting inflammatory mediators, including C-reactive protein, IL-6, IL-8, IL-1b, and TNF-a, which induce local inflammation and enhance oxidative stress.[17–23] EAT also secretes adipokines, such as adipokine activin A and matrix metalloproteinases 2 and 7, which have marked pro-fibrotic effects, inducing atrial fibrosis.[24,25] In addition, increased EAT volume is associated with adipocyte infiltration into the underlying atrial myocardium, resulting in atrial structural changes.[26–28] EAT modulates the activity of both parasympathetic and sympathetic autonomic nervous systems, primarily shortening the atrial refractory period, increasing the tendency for AF.[29,30] Local inflammation, oxidative stress, adipocyte infiltration, and autonomic nervous system modulation can lead to electrical and structural remodeling of the atrial tissue, contributing to development of AF.

EPICARDIAL FAT, AND TYPE AND SEVERITY OF ATRIAL FIBRILLATION

Numerous studies have demonstrated the association between EAT and the subtype of AF — paroxysmal and persistent, respectively.[31] Recent clinical studies have found a direct positive correlation between EAT and the persistence of atrial fibrillation. Patients with increased EAT were shown to have a more severe AF burden and were more likely to present persistent or chronic atrial fibrillation, as well as a higher rate of AF-related complications.[32–36] EAT has also been associated with left atrium (LA) volume, while no such association was encountered between systemic adiposity and LA volumes, suggesting the independent effect of pericardial visceral adiposity on the chronicity and severity of AF.[33] The presence of AF, AF chronicity, AF symptom severity, and recurrence of AF after ablation procedures have all been demonstrated to have significant associations with epicardial fat volumes, even after multivariate adjustments for body mass index, body surface area, and visceral adiposity.[33]

EPICARDIAL FAT DETERMINATION WITH NONINVASIVE IMAGING TECHNIQUES

EAT can be quantified with the use of noninvasive imaging techniques such as 2D transthoracic echocardiography (TTE), native cardiac computed tomography (CT), and magnetic resonance imaging (MRI).[37,38]

Transthoracic echocardiography is a low-cost, highly accessible noninvasive method to assess the thickness of EAT.[37] The method has been proved to be as useful as CT or MRI in the quantification of EAT.[37,39] On TTE, pericardial fat (PF) is presented as a hypoechogenic space between the myocardium and pericardium, and it should be considered increased if its thickness is over 5 mm during the end-diastolic period. The assessment is performed from the parasternal long axis view at the level of the free wall of the right ventricle.[37,40–43] Disadvantages of TTE include the high inter- and intra-observer variability, difficult image windows, and the uneven distribution of PF that could vary between the diastole and systole.[37,44]

Cardiac CT is a more precise technique for the assessment of EAT volume, total area, and thickness. Pericardial fat, which includes all fatty tissue within the pericardial sac, is illustrated with an image display threshold of –190 to –30 Hounsfield Units (HU).[37,44,45] CT advantages include the excellent intra-ob¬server and inter-observer variability and high resolution, and it also provides precise quantitative assessment of both volume and thickness of the pericardial and epicardial adipose tissue.[37,44–47] Concomitantly, CT can evaluate the presence of coronary artery disease and allows the measurement of the left atrium volume.[37,44] The main disadvantages of computed tomography are high costs and the exposure to ionizing radiation.[37,44]

Cardiac magnetic resonance imaging (CMRI) is the gold-standard imaging investigation for the assessment of the fatty tissue that surrounds the heart.[37] CMRI is a validated imaging method not only for the quantification of the adipose tissue that overlies the ventricular myocardium, but also for measuring the pericardial fat located in the vicinity of the atria, which might be more relevant in regard to the pathogenesis of atrial arrhythmias due to its close contact with the atrial myocardium.[44,48]

CMRI presents multiple benefits that include the quantitative assessment of left atrial volume for evaluating the functional and structural features of the ventricles and the

degree of fibrosis in the ventricular and atrial myocardium, which can all offer various information on the pathogenesis of AF and other arrhythmias.[48]

Besides allowing the acquisition of good quality images of the heart and the possibility of volumetric measurements on the pericardial adipose tissue, without additional exposure to radiation, CMRI is the single imaging modality that has been validated ex vivo for quantifying the epicardial fat. The main disadvantages of the method are the lack of feasibility in an emergency clinical setting and the increased costs.[37,44,48]

EPICARDIAL FAT — A NOVEL RISK PREDICTION MARKER

Epicardial adipose tissue has been linked with several acute coronary syndrome risk prediction scores.[49,50–52] The GRACE (Global Registry of Acute Coronary Events) score, the Syntax score for the severity of coronary lesions, and the clinical TIMI score for the prediction of adverse coronary events, have all shown positive correlations with an increased epicardial fat volume or thickness.[49,51,53] Similarly, an increased amount of fatty tissue surrounding the heart has been shown to predict major adverse cardiac events including myocardial infarction and death in subjects with acute coronary syndromes, as well as in those with suspected coronary artery disease.[54–56] The link between atrial fibrillation and EAT could be explained by the concomitant coronary artery disease of these patients. However, new research has shown that there is an association between AF and epicardial fat in subjects who are free of cardiovascular disease, independent of classical cardiovascular risk factors and coronary atherosclerosis.[57] The adipose tissue surrounding the heart has been shown to be independently associated with the incidence, severity, and recurrence of AF, but was also found to be a significant predictor for AF recurrence after catheter ablation for persistent AF and poorer ablation outcomes.[58,59] Further research is needed to prove the risk stratification properties of epicardial fat in atrial fibrillation, which could improve outcomes in these patients, beyond the already existing risk prediction clinical tools.

CONCLUSION

Epicardial adipose tissue has emerged as a novel biomarker reflecting the cardiovascular risk. Recent research on the pathogenesis and severity of atrial fibrillation has found PF as an independent predictor for the burden, persistence, and recurrence of atrial fibrillation, as well as for its related complications. Due to its noninvasive quantification, epicardial adipose tissue could represent a future imaging biomarker to be included among AF risk prediction tools.

CONFLICT OF INTEREST

Nothing to declare.

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