

The Relationship Between Pericardial Fat and Atrial Fibrillation

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Abstract

Pericardial adiposity is strongly associated with increased cardiovascular risk, especially for coronary artery disease. However, until 2010 researchers have not focused on the mechanistic role of pericardial fat in atrial fibrillation (AF) pathogenesis. Only a limited number of studies have reported on the significant association between pericardial fat and AF prevalence, and the role of pericardial fat on AF chronicity and symptom burden remain an ongoing debate. Several possible mechanisms associating pericardial fat with increased AF prevalence have been suggested, but no prior studies have definitively elucidated the precise role of pericardial adiposity on increased AF risk. Currently, pericardial fat has recently emerged as a new independent AF risk factor. In this brief review, we discuss several potential mechanisms that might associate pericardial fat to AF pathogenesis.

Introduction

Pericardial adipose tissue is associated with increased risk of cardiovascular disease, blood glucose level, systolic blood pressure, and hypercholesterolemia.^{1,2} Moreover, pericardial fat volume was greater in patients with high-risk coronary lesions compared to patients without coronary artery disease.³ However, the clinical significance of pericardial fat deposits in atrial fibrillation (AF) remains unclear.

Multiple studies have demonstrated that obesity contributes to increased AF prevalence and incidence.⁴⁻⁶ Long-term follow-up data of over 5,000 individuals in the Framingham Heart Study⁷ and nearly 48,000 subjects in the Danish Diet, Cancer, and Health Study⁸ showed that obesity is an independent AF predictor. Although many studies have evaluated the relationship between systemic mea-

sures of total body adiposity and AF, pericardial adipose tissue deposits have only recently been shown to be associated with AF.⁹ The pericardial adipose tissue deposit is correlated with body mass index¹⁰⁻¹² or visceral adipose tissue amount^{13, 14} in previous studies with multivariate analysis. In the present article, we review the relationship between the fat encircling the heart and AF.

Definition of Pericardial Fat

There seems to be confusion among clinicians and researchers on what "pericardial fat" actually means. Pericardial fat has to be distinguished from epicardial fat because epicardial and pericardial adipose tissue are anatomically different.¹⁵⁻¹⁷ Epicardial fat is located between the outer wall of the myocardium and the visceral layer of the pericardium. Pericardial fat is superficial to the epicardial fat and is therefore located between the visceral

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and parietal pericardia.¹⁸ Autopsy data showed that epicardial fat covers 80% of the heart's surface and constitutes 20% of the total heart weight. Epicardial fat is distributed along the coronary arteries, over the right ventricle (especially along the right border) and the anterior cardiac surface, and at the apex.¹⁹ The absolute amount of epicardial fat tissue is similar in the right and left ventricles. As a result, epicardial fat on the right side of the heart is three times thicker than that on the left side.¹⁹

However, distinguishing adipose tissue around the heart by conventional imaging modalities is a difficult process, and many studies have errantly defined "pericardial fat" as adipose tissue between the myoepicardium and the parietal pericardium.^{9,20-22} Therefore, in this review we use the term "pericardial fat" to define all adipose tissue present within the pericardial sac, and use the term "epicardial fat" when specifically referring to the fat located between the myocardium and the visceral pericardium.

Pericardial Fat Measurement

The growing appreciation of pericardial fat's importance in cardiovascular risk has led to interest in more directly quantifying different cardiac adipose tissue depots. Echocardiography, multidetector computed tomography (CT), and magnetic resonance imaging (MRI) are conventional imaging modalities that are well-suited for measuring pericardial fat amount. They have distinct advantages and disadvantages when compared with each other.

Echocardiographic measurement has several advantages, including its low cost, easy accessibility, rapid applicability, extreme safety, and good reproducibility.²³ Iacobellis et al. first proposed measuring the epicardial fat rather than the pericardial fat thickness. Epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. Pericardial fat thickness can be identified as the hypoechoic space superficial to the epicardial fat and parietal pericardium, and does not significantly change size during the cardiac cycle.¹⁴ This group also suggested that median values of 9.5 mm and 7.5 mm should be considered the threshold values for AF high-risk echocardiographic

fat thickness in men and women, respectively.²⁴ However, with echocardiography pericardial fat can only be measured over the right ventricle; this does not take into account fat distribution variations over the entire heart. Additionally, factors such as obesity may lead to a poor sonic window.

A significant advantage of CT over echocardiography is the capacity to provide a wide field-of-view of the entire chest. Unlike echocardiography and MRI, CT is capable of simultaneously providing information about coronary artery calcification, nonobstructive and obstructive coronary lesions, and the size and distribution of epicardial adipose tissue.²⁵ Disadvantages of CT include the use of intravenously-administered iodinated contrast material and exposure to ionizing radiation. Moreover, if CT is performed without ECG gating or triggering, as is often the case, imaged fat thickness can differ according to the cardiac cycle; thus cardiac motion artifacts can limit evaluation of the pericardium.²⁶

In an MRI test, the pericardial line was identified as a curvilinear line of low signal intensity between the high-intensity pericardial fat and the medium-intensity myocardium or high-intensity epicardial fat.²⁷ MRI is considered to be the gold standard in assessing visceral adipose tissue if imaging is performed with a fat-suppression technique. However, conventional MRI protocols are usually done without fat-suppression techniques, and fat and water both appear bright and are difficult to distinguish. It is also time consuming and costly to use MRI for only measuring pericardial fat.²⁸ Moreover, when using MRI with ECG gating, arrhythmias such as AF can cause imaging artifacts.

There is controversy regarding where and at what period during the cardiac cycle to optimally measure fat thickness. Iacobellis et al. suggested that fat thickness should be measured perpendicularly on the right ventricle free wall at end-systole in cardiac cycles, because this region is compressed during diastole.²³ However, others have measured fat thickness at the end-diastolic phase in the cardiac cycle.^{20, 29} Recent studies on pericardial fat are usually performed on patients at risk of cardiovascular disease utilizing the coronary CT protocol, so most measurements of pericardi-

al fat are performed during the diastolic phase.³⁰ Some studies did not use ECG-gated protocol.³¹ This can be more complicated, especially in AF patients, because of beat-to-beat variations that occur in AF hearts. Furthermore, the spatial distribution of adipose tissue adjacent to the myocardium is variable, which makes it difficult to use a single regional measurement as a representative surrogate of actual fat volume or distribution. Pericardial fat is mostly localized asymmetricaly in the perivascular AV or interventricular (IV) grooves.^{30, 32} Therefore, the exact regional distribution of fat may not be relevant, because there are no barriers in the pericardium separating the atria from the ventricles, thereby precluding local effects. Currently, most study groups measure pericardial fat thickness over the right ventricular free wall by echocardiography or by total fat volume using CT. However, it remains unclear whether measuring local pericardial fat thickness or pericardial fat volume is optimal.

Pericardial Fat and AF Prevalence

The role of pericardial fat on AF has not been a focus before 2010. Thanassoulis et al. reviewed the Framingham Heart Study, a middle-aged to elderly community-based cohort, and revealed that pericardial fat was associated with AF prevalence (odds ratio 1.30, 95% CI 1.05 to 1.60; $p=0.02$) even after adjusting for risk factors such as PR interval, hypertension, MI history, heart failure history, and body mass index.³³ Interestingly, significant AF-association was found only with pericardial fat, but not with total thoracic or visceral abdominal fat volumes.

In 2010, Chekakie et al. examined the association between pericardial fat and AF, and demonstrated a significant association of pericardial fat with both paroxysmal and persistent AF, completely independent of all major risk factors including age, hypertension, valvular heart disease, left ventricular function, obesity, and associated obstructive sleep apnea and LA enlargement.⁹ Pericardial fat volume was measured using CT in 273 patients. Among them, 76 patients showed sinus rhythm, 126 had paroxysmal AF, and 71 had persistent AF. Patients with AF had significantly more pericardial fat compared to patients without AF. Fat volume was associated with both par-

oxysmal AF (odds ratio 1.11, 95% CI: 1.01 to 1.23; $p=0.04$) and persistent AF (odds ratio 1.18, 95% CI: 1.05 to 1.33; $p=0.004$).

Batal et al. analyzed left atrial pericardial fat thickness by multi-slice CT in 169 individuals: 73 without AF, 60 with paroxysmal AF, and 36 with persistent AF. Left atrial epicardial fat pad thickness was measured in consecutive cardiac CT angiograms performed for coronary artery disease or AF. They reported that increased posterior fat pad thickness between the left atrium and the esophagus was associated with increased AF persistence, independent of age, BMI, and LA.³⁴ However, heterogeneity of baseline characteristics and no standard measurement criteria for quantifying atrial encircling fat volume were important study limitations.

Unlike the studies mentioned above using CT to measure pericardial fat, Wong et al. chose MRI as their tool and showed that patients with AF had greater pericardial fat volumes than reference patients in their study with 110 patients who underwent AF ablation. Adjusting for risk factors and weight, pericardial fat depots were individually predictive of the presence of AF (odds ratio 11.25, 95% CI: 2.07 to 61.24, $p=0.005$). Both periatrial fat (odds ratio 5.35, 95% CI: 1.30 to 2.19; $p=0.020$) and periventricular fat (odds ratio 10.94, 95% CI: 1.69 to 70.73; $p=0.012$) were predictive of AF.

Pericardial Fat and AF Outcome

Batal et al. mentioned about the relationship between epicardial fat over mid left atrium and atrial fibrillation burden in their work.³⁴ There is a positive relationship between epicardial fat thickness between the esophagus and the mid left atrium and prevalence of AF. Additionally, patients with persistent AF have a significantly thicker fat pad than those with paroxysmal AF.

Wong et al. remarked that there is a strong dose-response association, as assessed by AF chronicity and symptom burden.²⁰ Wong recruited 110 patients undergoing first-time AF ablation and underwent cardiac MRI a week before ablation. They also demonstrated that pericardial fat was an independent predictor of AF recurrence after ablation.²⁰ This was the first study relating AF ablation

outcome with pericardial fat, but it was a cross-sectional study design and had limitation of causality.

Possible Mechanisms of Pericardial Adiposity-Induced AF

Adipose tissue is a highly active organ that secretes numerous peptides such as cytokines, chemokines, and hormone-like proteins.³⁵ Pericardial fat is located adjunct to the cardiac chamber wall and the epicardial fat and myocardium share the same blood supply. Therefore, they may be able to interact with each other not only biochemically but mechanically.

Inflammation

Recent studies have strongly implicated inflammation in the genesis and maintenance of atrial arrhythmias.³⁶⁻⁴¹ Electrical remodeling by inflammation with resultant atrial refractoriness abbreviation and shortening of the action potential duration appears to be responsible for the self-perpetuation of AF. Structural remodeling by inflammation, with features of interstitial fibrosis and cellular degeneration, may also provide a susceptible substrate that promotes reentrant circuits and AF.⁴² From the strong association between AF, obesity, and inflammation, and given the inflammatory characteristics of pericardial adipose tissue in its relationship to cardiovascular disease,^{1,43,44} we can speculate that pericardial fat is associated with AF prevalence and maintenance. In 1996, histopathologic studies of lipomatous septal hypertrophy demonstrated an inflammatory infiltrate associated with myocardial fibrosis that surrounded infiltrating adipose tissue.⁴⁵ Mazurek et al. suggested that pericardial fat was associated with increased local expression of inflammatory markers in 2003.⁴⁶ Pericardial fat is an important local source of inflammatory mediators including tumor necrosis factor- α and interleukin-6,⁴⁶ which may have direct arrhythmogenic effects on atrial tissue and have associations with AF initiation.⁴⁷⁻⁴⁹ Chekakie et al. proposed that the local effects of inflammatory cytokines released from the pericardial fat may be a potential mechanism of the pathogenesis of AF.⁹ In summary, pericardial adipose tissue is directly contiguous with atrial and ventricular myocardium, and it releases inflammatory cytokines. These local inflammatory effects may provide a mechanism to explain the association between AF and

pericardial fat. However, this hypothesis needs to be addressed in future studies.

Fatty Acid Cardiotoxicity and AF

Pericardial fat maintains fatty acid homeostasis in the coronary microcirculation, wherein there exists a high basal rate of fatty acid uptake into these blood vessels.⁵⁰ Given the known toxicity of excess fatty acids on cardiomyocytes, epicardial fat may blunt fatty acid-induced cardiotoxicity by acting as a reservoir for these potentially toxic molecules.^{51,52} However, this hypothesis has not yet been thoroughly evaluated by in the AF population.

Left Atrial Enlargement and AF

Vaziri et al. reported that left atrial (LA) enlargement is an important precursor of AF.⁵³ Teresa et al. showed that a larger LA volume is associated with a higher AF risk in older patients.⁵⁴ Osranek et al. revealed in a prospective study that LA volume is a strong and independent predictor of post-operative AF.⁵⁵ Recent studies confirm that pericardial fat is associated with LA dimensions.^{20,22,56-58} Investigators tried to explain the mechanism how pericardial fat affects LA dilatation. Fat deposit subepicardially in the free walls or atria and around the appendage and possible local interactions between these tissues could be the clue. However the pathogenic mechanism of these alterations is not well known yet and most studies included obese people as those subjects. Thus, the evidence is strong that left atrial enlargement, including adiposity, correlates with an increased AF risk.

Elevated End-Diastolic Filling Pressures that Lead to Atrial Dilatation and AF

Obesity is an important and modifiable AF risk factor, and is associated with left ventricular (LV) diastolic dysfunction.⁷ Diastolic dysfunction is known to be a strong predictor of LA remodeling and may contribute to electrical instability.⁵⁹ This is because diastolic dysfunction causes atrial pressure and volume overload, leading to structural remodeling. Previous studies revealed that diastolic dysfunction appears to be a potent precursor of AF.⁶⁰ Recently, Iacobellis et al. showed that increased pericardial fat is associated with

significantly impaired LV diastolic function.⁵⁷ Theoretically, Accumulation of fat pads around ventricles may theoretically increase ventricular stiffness and thus contribute to diastolic dysfunction within a poorly distensible pericardium.⁶¹ Some possible mechanisms were suggested that that the increased epicardial fat mechanically affects LV and RV diastolic filling and consequently induces atria enlargement.⁶² Thus, there appears to be a significant correlation between end-diastolic filling and AF. Impaired diastolic function might be a result of excessive pericardial adiposity.

Pericardial Fat and the Autonomic Nervous System

Thanassoulis et al. suggested that increased pericardial fat could locally influence autonomic ganglia, thereby enhancing vagal tone and increasing AF propensity.³³ Intrinsic autonomic nervous system modulation increases AF propensity. Animal models have demonstrated that parasympathetic nerve activity within cardiac fat pads promotes AF, primarily by shortening the atrial refractory period.^{63,64} Batal et al. supposed the additional involvement of cardiac fat pad parasympathetic ganglia in their study.³⁴ However, reports on the implication of the epicardial anterior fat pad on postoperative AF patients have had conflicting results that maintaining the fat pad prevented attenuation of parasympathetic tone after CABG but does not reduce postoperative AF.⁶⁵ Epicardial fat pad ablation in canine models did not suppress AF inducibility in the long term.⁶⁶ Taken together, the role of the autonomic nervous system in pericardial fat-mediated AF remains to be conclusively determined.

Coronary Artery Disease

Coronary artery disease is present in over 20% of AF patients.^{67, 68} But whether atrial ischemia predisposes to AF and how AF is modulated by coronary perfusion are uncertain.⁶⁹ Recently, there has been incremental evidence supporting a relationship between pericardial fat levels and coronary artery disease.^{3,31,70} Increased epicardial fat appears related to cardiac microvascular

dysfunction, as detected by a correlatively reduced coronary blood flow reserve.⁷¹ White et al. think that atrial flow reserve limitation may lead to atrial ischemia, fibrosis, and, thereby, perpetuation of the arrhythmia.⁷² Connecting pericardial fat, atrial flow reserve, and AF will be an important future task.

Future Considerations

Pericardial fat has recently emerged as a new independent AF risk factor.⁷³ However, studies on AF prevalence or on the role of pericardial fat in AF pathogenesis are lacking. Further investigations are required into this clinically relevant association, and will provide a better understanding of AF burden and outcome.

The possible positive effects of fat tissue also require consideration. Pericardial adipose tissue has both inflammatory and anti-inflammatory characteristics.⁷⁴ Especially, epicardial fat is abundant of adiponectin and adrenomedullin, adipokines with anti-inflammatory properties that could locally modulate heart physiology and exert a protective effect through induction of anti-inflammatory cytokines.^{75,76} Other studies have suggested that increased epicardial adiponectin is associated with maintenance of sinus rhythm following cardiac surgery.⁷⁷ These researchers think that regulating the inflammatory mediator balance in pericardial adipose tissue may have an important role in AF prevention.

There are racial differences in AF prevalence. Borzecki et al. reported that, even after adjusting for risk factors, African Americans appear to be at a lower AF risk than Caucasians.⁷⁸ Howard et al. reported that non-Hispanic Caucasians have more epicardial and pericardial fat than do African Americans.⁷⁹ Although pericardial fat deposit heterogeneity among races in relation to AF prevalence has not yet been studied, this is an attractive and potentially important focus of future research.

Conclusions

Obesity is a well-known and important AF risk factor, though the relationship of AF and local peri-

cardial fat has not yet been fully elucidated. Standardized definitions and measurement methods for pericardial fat remain to be consensually arrived at. Although limited in number and scope, recent studies strongly suggest that extensive pericardial fat deposits are related to increased AF prevalence and a worse clinical outcome. To date, the propagative mechanisms of pericardial fat accumulation on AF pathogenesis remain controversial, although numerous hypotheses have been put forth and discussed. Prospective, randomized, and thoughtfully-designed trials will reveal the strongly suggested role of pericardial fat in AF.

Disclosures

No disclosures relevant to this article were made by the authors.

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