The Role of Pericardial and Epicardial Fat in Atrial Fibrillation Pathophysiology and Ablation Outcomes

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Abstract

Emerging evidence suggests that epicardial and pericardial fat are related to the presence, severity and outcome of AF. These associations, independent of generalized obesity, suggest that they may become increasingly useful as markers for risk stratification or monitoring in the clinical setting. Mechanistically, studies have suggested the effects of epicardial and pericardial fat may be mediated by local adipokines, inflammation, fatty infiltration, modulation of AF drivers and left atrial dilatation. Given the dual epidemics of AF and obesity, in the present paper we review the role that the ectopic adipose tissue surrounding the heart has in the pathogenesis of AF. Further inquiries in this active area of investigation may ultimately lead to new insights in how to best combat these interrelated epidemics and reduce the societal burden of AF.

Introduction

In recent years, the widespread availability of noninvasive imaging techniques has allowed for increasing insights into the role that ectopic fat plays in cardiovascular disease. This present review discusses our current knowledge regarding the relationship between ectopic fat surrounding the heart and atrial fibrillation (AF). In particular, the role that such adipose tissue, the related pericardial and epicardial fat depots, have in the pathogenesis and outcome of AF will be reviewed.

The Interrelated Epidemics of Atrial Fibrillation and Obesity

Numerous contemporary reports have described a rising prevalence of AF that is expected to continue.[1-3] It has been predicted that there may be almost 16 million individuals with AF in the United States alone by 2050.[2] Whilst the overall prevalence of AF is approximately one percent, this is greater in older individuals and rises to nine percent in those over 80 years of age.[4] Given the ageing population structures in developed countries, a growing number of individuals are likely to be affected by the significant symptoms, impaired functional status and poorer quality of life that AF is associated with, primarily as a result of congestive cardiac failure and embolic stroke. Such complications can lead to excessive health service utilization,[5,6] and ultimately increased mortality.[7,8] It is clear that AF is a growing clinical and public health concern, and represents a significant burden on both the

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individuals it affects and society as a whole. Furthermore, once AF develops, management strategies aimed at eliminating AF are of limited success and not without risk.[9,10] Even when treatment is apparently successful, the risk of stroke may not be eliminated.[11] As a result, the identification and management of modifiable risk factors for AF is of great importance.

Whilst traditional risk factors for AF such as hypertension, ischemic heart disease, congestive cardiac failure and structural heart disease are well-known, obesity is becoming increasingly recognized as a novel risk factor that may be contributing to the growing prevalence of AF. Several prospective studies have reported significant associations between obesity and incident AF.[12-17] The Framingham Heart Study showed that each additional unit of body mass index (BMI) conferred a 4% increase in the risk of developing AF.[13] Investigators from the Danish, Diet, Cancer and Health Study reported that each additional unit of BMI was associated with a 8% and 6% increase in the risk of AF over 5 years in men and women.[12] Dublin and colleagues reported that the association with BMI was stronger for sustained AF than for transitory or intermittent AF.[15] Data from a multicenter registry showed that increasing height and body surface area was also associated with AF risk.[16] Given the link between obesity and obstructive sleep apnea, Mayo Clinic researchers investigated the two conditions with regards to AF risk and found them both to be independent risk factors.[17] Large body size in youth has also been shown to be associated with the development of later AF.[18] Data from the Women's Health Study has recently suggested that not only was BMI associated with AF risk, but also that dynamic, short-term increases in BMI conferred greater risk.[14] In a meta-analysis of five population-based cohorts, baseline BMI was associated with a graded risk of AF.[19] Furthermore, obesity has been shown to be a risk factor for paroxysmal AF progressing to more permanent AF.[20]

The Importance of Regional Body Fat Distribution

The traditional measurement of obesity has been BMI and, as mentioned previously, a number of prospective studies have described relationships between BMI and cardiovascular disease mor-

bidity and mortality. Although it remains a useful clinical and epidemiologic parameter, the observation that individuals with similar BMI may exhibit significant variation in cardiovascular risk has fuelled an increasing interest in body fat distribution.[21,22] This initially began with the measurement of waist circumference and, later, waist-to-hip ratio as alternative measures of body fat distribution. Studies reporting stronger correlations of these measures with cardiometabolic outcomes lent weight to the theory that it was regional body fat distribution, rather than simply excess fat overall, that was more important in cardiovascular disease risk.[23, 24]

Waist circumference and waist-to-hip ratio remain in many obesity assessment guidelines given the ease in which they can be applied in the clinical setting and incremental predictive information they provide in conjunction with BMI. From a mechanistic point of view, however, they are limited in that they are unable to distinguish between the subcutaneous and visceral adipose tissue compartments. The widespread availability of imaging techniques, particularly, computed tomography (CT) and magnetic resonance imaging (MRI) has allowed for the separate quantification of these compartments. As a result, this has led to a number of studies examining the association between these ectopic visceral fat depots and cardiovascular disease.

Epicardial, Paracardial and Pericardial Fat

The terms epicardial fat, paracardial and pericardial fat, have been used interchangeably throughout the literature, despite differences in location and function. They are often collectively referred to as cardiac ectopic fat or cardiac adipose tissue. Pericardial fat consists of two layers: the visceral, epicardial fat layer and the parietal, paracardial fat layer. Epicardial fat is adipose tissue layer situated between the myocardium and visceral pericardium. Paracardial fat is the adipose tissue layer located external to the parietal pericardium. Give the different embryological origins and vascular supply of these two fat depots, there is reason to suspect they may have distinct biochemical properties. However, there is a lack of standardized nomenclature and few reports have individually studied each depot in relation to metabolic parameters and outcomes. Keeping this in mind,

in this section, we will nevertheless discuss individual fat depots as defined by the authors of each study.

Cardiac Ectopic Fat and the Presence and Severity of Atrial Fibrillation

Investigators first suspected that that cardiac ectopic fat may be associated with atrial arrhythmias in the 1960s and 1970s.[25-28] Without the availability of modern imaging techniques, it was recognized in necropsy observations that some individuals demonstrated prominent amounts of fatty deposits both in the interatrial septum and in the epicardial space. It was hypothesized that 'lipomatous hypertrophy' of the interatrial septum might interrupt electrical pathways to facilitate atrial arrhythmogenesis.[29]

In recent years, a number of studies that were able to accurately quantify cardiac ectopic fat using modern imaging techniques were published almost simultaneously. These described similar associations between fat layers surrounding the heart and the presence and chronicity of AF and, taken together, have provided suggestive evidence supporting a relationship between the two entities.

In one study, Al Chekkaki and investigators analyzed CT scans from 273 individuals.[30] Pixels within the pericardial sac with Hounsfield units of -190 to -130 were defined as adipose tissue. In this way, they were able to measure total pericardial fat volume and found that this was greater in persistent AF patients compared to those with paroxysmal AF, and those with any AF compared to those without AF. These associations persisted after adjusting for potential confounders, including BMI. In the largest study to date, Thanassoulis and other colleagues studied CT scans from 2317 participants in the Framingham Heart Study Offspring and Third Generation Cohorts.[31] Similar to Al Chekkaki et al, the Framingham investigators defined total pericardial fat volume as adipose tissue within the pericardial sac with Hounsfield units -195 to -45. A particular strength of this study is that both intrathoracic fat, defined as all other adipose tissue within the thorax, and visceral adipose tissue, defined as visceral fat within the abdominal cavity, were quantified volumetrically in addition to pericardial fat. After adjusting for

other AF risk factors, total pericardial fat, but not intrathoracic or visceral fat, was associated with prevalent AF.

Other studies have sought to explore whether adipose specifically surrounding the atria is related to AF. Batal and colleagues assessed 169 consecutive individuals who had had CT angiograms for either coronary artery disease or AF.[32] They measured the thickness of peri-atrial epicardial fat in short-axis view at the mid-left atrium, and found that peri-atrial epicardial fat thickness was associated greater in patients with AF compared to those without. Similar to previously discussed studies, they also found that peri-atrial epicardial fat thickness was greater in persistent AF than in paroxysmal AF. These associations persisted after adjusting for potential confounders, including BMI. Whilst one limitation of this study was that they were unable to perform volumetric analysis to quantify fat volumes, a potentially important fact given conflicting data regarding the correlation between epicardial fat thickness and volume,[33] others studies reporting volumetric data have provided corroborating evidence. Instead of using CT, our group used cardiac MRI to quantify peri-atrial, peri-ventricular and total pericardial fat volumes in 130 individuals.[34] We found that peri-atrial fat volumes, but not measures of generalized adiposity such as BMI or body surface area, were predictive of the presence and increasing chronicity of AF. These associations persisted even after multivariable adjustment, including that for body weight. In another study, Tsao and colleagues used CT images to describe the regional distribution of epicardial fat surrounding the left atrium in 102 patients.[35] They similarly found that patients with AF had a significantly increased volume of epicardial fat surrounding the left atrium, and there was a trend for patients with persistent AF to have greater volumes compared to those with paroxysmal AF. In comparison, BMI was not significantly different between patients with or without AF. Shin and investigators also used CT imaging to study the regional distribution of epicardial fat in 80 subjects.[36] In addition to finding that epicardial fat volumes increased with greater chronicity of AF, they found that the thickness of peri-atrial epicardial fat, as measured at the atrioventricular groove and inter-atrial septum, was greater in AF patients. These studies have suggested that ectopic fat surrounding the atria may be more predictive

of the presence and chronicity of AF than generalized adiposity. Whether peri-atrial fat is more predictive than peri-ventricular fat remains unclear. Shin and colleagues found that peri-ventricular fat thickness over the right ventricular free wall was not significantly different between patients with and without AF.[36] However, epicardial fat thickness may not be reflective of epicardial fat volume,[33] and in comparison, we found that both peri-atrial and peri-ventricular fat volumes were predictive of the presence of AF.[34] In addition to the observed associations between pericardial/epicardial fat and the presence and chronicity of AF, our also group found that measures of pericardial fat volume were also associated with increased symptom severity.[34]

Potential Arrhythmogenic Mechanisms

Visceral ectopic fat depots are thought to exert systemic and local effects.[21] Fat depots such as visceral adipose tissue, intrahepatic fat/fatty liver and intramuscular fat have been shown to be associated with a number of systemic metabolic derangements, supporting the theory of their systemic pathological effect.[37,38] The proximity of these fat depots to organs involved in insulin, glucose and lipid metabolism are speculated to facilitate these derangements. In contrast, fat depots such as epicardial fat, pericardial fat, perivascular fat and renal sinus fat are thought to have local toxic effects.[21] With regards to investigations pertaining to epicardial and pericardial fat, a number of studies provide increasing mechanistic evidence. Epicardial fat is a source of various inflammatory mediators and other bioactive molecules.[39] As an endocrine and paracrine organ, in this way it has been hypothesized that released adipokines and free fatty acids could directly influence the adjacent myocardium and coronary arteries. Similarly, epicardial fat has been demonstrated to have significant elevations in inflammatory infiltrates compared to subcutaneous fat, and the presence of lymphocytes, macrophages and mast cells.[40] Epicardial fat also demonstrates greater expression of key inflammatory signaling molecules such as inflammatory-nuclear factor kappaB and c-Jun N-terminal kinase activity compared to subcutaneous fat.[41] Others have also shown via proteomic analysis higher levels of reactive oxygen species and lower levels of catalase in epicardial fat compared to subcutaneous fat.[42]

It has been previously suggested by epidemiologic studies that the relationship between body mass index and AF may be mediated by changes in cardiac structure.[13] However, there is also considerable evidence linking epicardial and pericardial fat with cardiac structure. Pericardial fat volumes have shown to be independent predictors of left atrial diameter and volume.[34,43] Others have described infiltration of fat into the atria and ventricles and a correlation between epicardial fat and myocardial fat content by magnetic resonance spectroscopic.[44-46] Such structural lipid remodeling could lead to heterogenous conduction and non-uniform anisotropy, predisposing to arrhythmogenesis.[47-50] Furthermore, structural lipid remodeling and a mechanical effect of overlying adipose tissue might influence left atrial function.[51]

Cardiac Ectopic Fat and Atrial Fibrillation Ablation: Further Mechanistic Insights

Since the relationship between cardiac ectopic fat and AF has become apparent, a few investigators have studied the relationship between epicardial or pericardial fat and AF ablation outcomes. Our group found that MRI-measured pericardial fat volumes was associated with an earlier AF recurrence following radiofrequency catheter ablation in a cohort of 110 patients with paroxysmal, persistent and permanent AF.[34,35] Similarly, Tsao studied 68 patients with paroxysmal and persistent AF and found that CT-measured epicardial fat volume surrounding the left atrium was associated with AF recurrence.[35] Finally, Nagashima reported that CT-measured epicardial fat volume surrounding the left atrium was associated with AF recurrence in a cohort of 40 patients with paroxysmal and persistent AF.

In addition to those discussed in the preceding section, the findings of the above studies provide further insight into possible mechanisms underlying the relationship between epicardial fat, pericardial fat and AF. Cardiac ectopic fat contain numerous ganglionated plexi that have long been hypothesized to facilitate the occurrence of atrial fibrillation via their role in the cardiac autonomic nervous system.[52] Studies have shown, albeit vari-

ably, that ablation of ganglionated plexi may potentially reduce AF inducibility.[53,54] Consistent with this, one recent report described how epicardial fat correlated anatomically with endocardial sites of high dominant frequency, suggesting a potential role in supporting AF drivers.[55] Another recent study found that obese patients had significantly shorter effective refractory periods in the left atrium and pulmonary veins than normal weight individuals, though epicardial or pericardial fat was not measured.[56] Put together, these lines of evidence suggest additional neural mechanisms may link pericardial/epicardial fat and AF; patients with greater amounts of ectopic cardiac fat may have increased intrinsic adrenergic and cholinergic nerve structures within ganglionated plexi.[57]

Effect of Weight Reduction on Cardiac Ectopic Fat

To date, there are few studies assessing the effect of weight loss on epicardial or pericardial fat. A well-conducted recent study in bariatric surgery patients, however, provides key initial information. In this study, investigators used measured epicardial fat volumes using MRI, in addition to CT-measured visceral abdominal fat and standard BMI.[58] They found that bariatric surgery significantly reduced epicardial fat volumes. Interestingly, the decrease in epicardial fat volumes was not correlated with the decrease in visceral abdominal fat or BMI, suggesting heterogenous effects of weight loss on differing fat depots. Whilst no published reports exist on weight loss and cardiac ectopic fat in patients with AF yet to the best of our knowledge, preliminary data from our group suggests that weight loss may potentially reverse obesity-related electrical and structural remodeling, and improve AF symptoms.[59, 60]

Conclusions

Emerging evidence suggests that epicardial and pericardial fat are related to the presence, severity and outcome of AF. These associations, independent of generalized obesity, suggest that

they may become increasingly useful as markers for risk stratification or monitoring in the clinical setting. Mechanistically, studies have suggested the effects of epicardial and pericardial fat may be mediated by local adipokines, inflammation, fatty infiltration, modulation of AF drivers and left atrial dilatation. Given the dual epidemics of AF and obesity, in the present paper we review the role that the ectopic adipose tissue surrounding the heart has in the pathogenesis of AF. Further inquiries in this active area of investigation may ultimately lead to new insights in how to best combat these interrelated epidemics and reduce the societal burden of AF.

Disclosures

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

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