



## Epicardial Fat and Atrial Fibrillation: A Review

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### Abstract

Atrial fibrillation (AF) is a progressive disorder that increases with age. Obesity is an important risk factor for AF. Pericardial fat is an active adipose tissue in close proximity to the heart and has been shown to be a risk factor for structural as well as coronary artery disease independent of body mass index. Recent studies suggest a role of epicardial fat in atrial remodeling as well as AF burden. This review will summarize the recent evidence linking epicardial fat and AF.

### Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality.<sup>1</sup> Obesity is associated with cardiovascular disease, including AF.<sup>2,4</sup> Visceral adipose tissue is thought to play a more central role in the development of cardiovascular disease as opposed to subcutaneous adipose tissue.<sup>5</sup> Pericardial fat is an active adipose tissue in close proximity to the heart and has been shown to be a risk factor for structural as well as coronary artery disease independent of body mass index.<sup>6, 7</sup> This review will summarize the recent evidence associating epicardial fat with AF.

### Anatomical Definitions

The heart is covered by two sacs: The first is the fibrous pericardium, and the second is the serous pericardium which consists of two components: the visceral pericardium and the parietal pericardium. The space between the myocardium and visceral pericardium is the epicardial space and epicardial fat is defined as the fat lying within that space. On the other hand, pericardial fat is fat located within the pericardial sac, which is the border between the pericardial and intrathoracic fat.<sup>8</sup> Epicardial fat covers 56-100% of the hearts sur-

face in humans, and mostly is present over the atrioventricular groove, the right ventricular free wall and along the course of the coronary arteries.<sup>9</sup> It is hard to dissect the epicardial fat entirely off the myocardium; this is especially true on the atrial surface.<sup>10, 11</sup> This is an important limitation of autopsy studies, and most of the description of epicardial fat distribution on the atria comes from imaging studies that measured atrial fat distribution as well as thickness. At the atrial level, the epicardial fat is mostly located near the roof of the left atrium, near the left atrial appendage and lateral to the mitral isthmus, and is more in the superior half of the left atrium compared to the inferior half of the left atrium.<sup>12</sup> Given the inability of current imaging modalities to distinguish epicardial from pericardial fat, most of the epidemiological studies as well as the clinical studies focusing on AF in this review have measured pericardial fat,<sup>13, 14</sup> which is the fat located within the fibrous pericardial sac. This can lead to overestimation of the epicardial fat volume, an important limitation of all imaging modalities.<sup>15</sup> Even though the authors might have measured the adipose tissue volume and thickness within the fibrous pericardial sac; in this review, we kept the description terms used by the authors in their original articles.

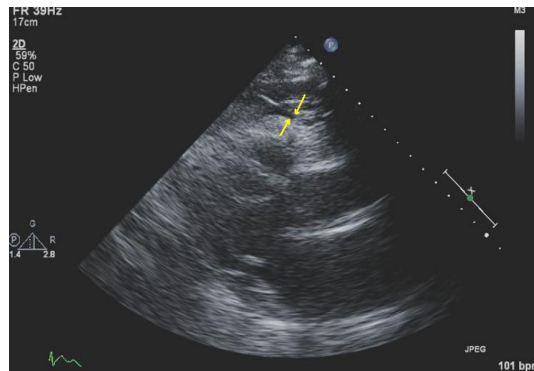
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## Measurements of Epicardial Fat

### 1- Two Dimensional Echocardiography

There are several imaging modalities that mea-

**Figure 1:** The PLA view, perpendicular measurements are taken between the RV wall and the visceral pericardium at end systole. Epicardial fat is the hypoechoic area between the myocardium and visceral pericardium (between the yellow arrows).



Most of the epicardial fat is located in the atrioventricular groove and interventricular groove, and is at times unevenly distributed around the atria and ventricles. In an effort to make the measurements more reliable and reproducible, epicardial fat thickness is measured in two standard views, the parasternal long axis (PLA) as well as the parasternal short axis views (PSA views). All measurements are done at end systole (when the aortic valve is open) in three cardiac cycles. In the PLA view, perpendicular measurements are taken between the RV wall and the visceral pericardium (Figure 1). In PSA view, the epicardial fat is measured at the midventricular level between the RV wall and the visceral pericardium. This method has been used in several studies linking obesity and epicardial fat and has excellent intraobserver as well as interobserver variability (ranging from 0.90 to 0.98 and from 0.93 to 0.98 respectively). There is no upper limit of normal that has been formally defined, but in general the epicardial fat thickness ranges between 1 and 23 millimeters (mm). The echocardiographic measurement of epicardial fat thickness has several advantages, including the widespread availability of 2 D Echo, its low cost and the measurements are easy and can be done offline. Disadvantages include relying on thickness on two perpendicular views, which doesn't always account for the variation in the distribution of the epicardial fat. Furthermore, the thickness of the epicardial fat is not uniform in the PLA views, and could vary between end systole

sure epicardial fat, with some measuring the thickness and others measuring the total volume. Using two-dimensional echocardiography (2 D Echo), Iacabellis et al. measured the epicardial fat thickness as a measure of visceral adiposity.<sup>16-18</sup>

and end diastole. Some patients have difficult windows and it is usually hard to distinguish the visceral pericardium, which makes it hard to differentiate between epicardial and pericardial fat. It is our view that this modality suffers from the same limitations that computed tomography and magnetic resonance imaging have when it comes to differentiation between epicardial and pericardial fat, and that most of the measurements used could have easily been for pericardial fat thickness, not epicardial fat thickness, since it is hard to identify the visceral pericardium and it is easier to identify the fibrous pericardial sac.

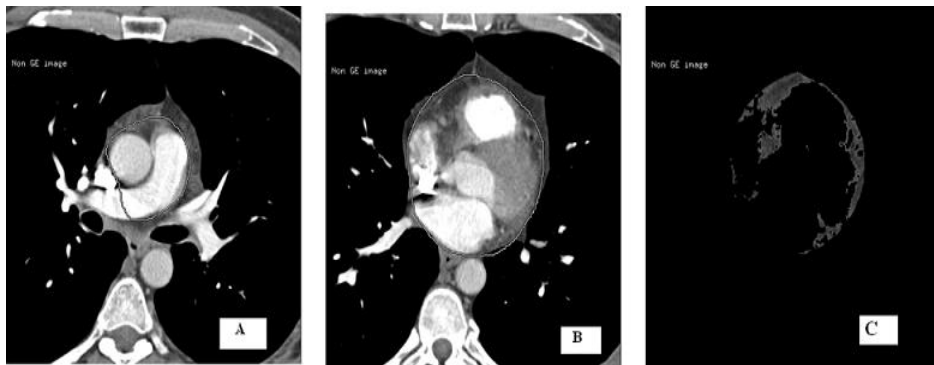
### 2-Multidetector Computed Tomography (MDCT)

The Computed tomography offers a more accurate way of measuring both pericardial fat thickness and volume. The pericardial fat is mostly located in the atrioventricular and interventricular grooves, with the thickest area being usually the right atrioventricular groove with a mean thickness of  $5.3 \pm 1.6$  mm. A study by Batal et al measured periatrial fat thickness by having the CT plane in the mid LA and measuring the epicardial fat thickness between the LA and the esophagus (LA-ESO), LA and thoracic aorta (LA-TA) and LA and pulmonary artery (LA-PA). In the total population, including controls, patients with paroxysmal as well as persistence AF, the median LA-PA thickness was 65 mm, the median LA-ESO

thickness was 40 mm and the mean LA-TA thickness was 58 mm. Using these parameters, the authors found that epicardial fat in close proximity to the esophagus was most significantly associated with AF burden.<sup>19</sup> In another study on epicardial fat and AF, Tsao et al. measured epicardial atrial fat volume near as well as regional distribution around the left atrium. They found that epicardial

fat is unevenly distributed around the LA and is mostly found in three areas: first is within the superior vena cava, right pulmonary artery and right sided roof of the LA (29.8%), within the aortic root, Main pulmonary artery and LA appendage (26.5%) and between the left inferior pulmonary vein and the left AV groove (18.1%).<sup>12</sup>

**Figure 2:** The pericardium is usually manually traced from slices starting at the pulmonary artery bifurcation (A), slice by slice (B) and pericardial fat consists of all adipose tissue within the pericardial sac, identified by an image display threshold setting of -190 to -30 Hounsfield Units (C).



Most of the other studies on the association between pericardial fat and coronary artery disease (CAD) and AF focused on calculating total pericardial fat volume. CT studies were performed using a 16 or 64-slice scanner. Gated studies are performed using an electrocardiogram-triggered scanning protocol. To ensure adequate gating and minimal motion artifact, patients in AF could receive beta-blockers and have CT scanning only if the ventricular response was <80 beats/min. The percentage of the R-R interval with the least amount of motion was used for pericardial fat measurements, which are performed offline using a semi-automated technique and dedicated workstation (Figure 2). Contiguous 2.0-mm or thinner slices of the heart extending from the bifurcation of the pulmonary artery to the diaphragm are analyzed. The pericardium is usually manually traced, and pericardial fat consisted of all adipose tissue within the pericardial sac, identified by an image display threshold setting of -190 to -30 Hounsfield Units (HU),<sup>13</sup> with some studies using a threshold of -200 to -50 HU.<sup>12</sup> The studies reported excellent intraobserver as well as interobserver variability (ranging from 0.95 to 0.98 and 0.96 to 0.99 respectively).<sup>12, 13</sup> MDCT offers several advantages; it has a great spatial resolution, it allows accurate measurements of LA volume, and it allows for measurements of both

thickness and volume of pericardial fat at the same time. However, it is expensive, not always clinically available and is associated with radiation and contrast exposure to the patient. Motion can make it very hard to measure the pericardial fat, and in patients with AF and high ventricular rates, it might be difficult to obtain a good study.

### 3-Magnetic Resonance Imaging

The only study on pericardial fat and AF to use Magnetic Resonance Imaging (MRI) for measurement is the study by Wong et al. They also looked at ablation outcomes. In this study, MRI at 1.5 T was used and measurements of epicardial fat were done offline as done with CT. The areas of fat were traced on consecutive end diastolic short axis images and multiplied by the thickness to obtain the total volume. Periatrial fat was defined as fat close to the LA, while periventricular fat was defined as fat close to the ventricles. Total pericardial fat is the total fat volume between the myocardium and parietal pericardium. The slices used could be up to 6 mm in thickness. MRI has several advantages including measuring LA volume, left and right ventricular structure and function, and is considered by some to be the gold standard to measure visceral adipose tis-

sue. The MRI has lower spatial resolution when it comes to the Z axis, and similar to MDCT; is expensive, not readily available in all centers and motion can make it difficult to measure pericardial fat volumes. The coefficient of variation for intraobserver and interobserver variability in this study was excellent (3.5 to 4.5% respectively).<sup>20</sup>

### Epicardial Fat as an Active Tissue

Visceral adipose tissue is metabolically active and is thought to play a more central role in presence and development of cardiovascular disease as opposed to subcutaneous adipose tissue.<sup>5</sup> Epicardial fat is thought to have properties similar to visceral fat.<sup>21</sup> It has twice the capacity of synthesizing fatty acids compared to popliteal fat and it has a higher capacity of fatty acid breakdown. This allows it to maintain the local fatty acid concentration and protects the heart from a toxic level of fatty acids that can depress contractile function.<sup>22</sup> It acts as a buffer for the heart against hypothermia.<sup>24</sup> In fact this insulating effect is also important during ablation procedures, since epicardial fat is a poor conductor of current. Epicardial fat has very slow electrical conductivity and can impede the passage of the radiofrequency current, making the epicardial ablation lesions ineffective, even when using cooled electrodes. Using mathematical modeling for radiofrequency ablation lesions on the epicardial surface of the atria, Suarez et al. found that as fat thickness increased, the maximum tissue temperature and the lesion depth decreased, regardless if dry or cooled electrodes were used.<sup>25</sup> This could be the reason why 25-30% of the surgical epicardial ablation lesions are non-transmural.<sup>26</sup> The slow conducting properties of the epicardial fat could have a protective effect on the esophagus when delivering endocardial ablation lesions on the posterior wall of the left atrium, but this was not formally studied. Furthermore, epicardial fat can influence the depth and size of ablation lesions delivered on the epicardial surface of both atria and ventricles and can be the cause of the failure of ablation on the epicardial surface of the heart.<sup>27</sup> Epicardial fat is also an active tissue and secretes pro and anti inflammatory mediators including Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Interleukin-6 (IL-6), Monocyte Chemoattractant Protein-1 (MCP-1), Leptin and Plasminogen activator inhibitor-1.<sup>28-30</sup> Epi-

cardial fat can affect the heart in different ways; compression of the heart by large epicardial fat volumes can lead to impaired diastolic filling and increased left atrial dimensions. Furthermore, the pro and anti inflammatory cytokines secreted by the epicardial adipose tissue can act locally in a paracrine fashion or can act downstream when secreted into the vasa vasorum. Zhou et al. studied samples of pericardial fat from patients undergoing coronary artery bypass graft surgery as compared to samples from epicardial fat in non-CAD patients and in samples of subcutaneous fat surrounding the saphenous veins. Histological samples showed increased macrophage infiltration into the epicardial fat, decreased adiponectin expression shown by reverse transcriptase polymerase chain reaction (RT-PCR) and enhanced expression of IL-6 and TNF- $\alpha$  in epicardial adipose tissue in patients with coronary artery disease as opposed to epicardial fat in non-CAD patients or in subcutaneous fat around the saphenous vein in patients with CAD.<sup>5</sup> AF is associated with inflammation. Recent studies have demonstrated a high prevalence of inflammatory infiltrates and fibrosis in atrial biopsies of patients with lone AF.<sup>31</sup> Population studies have demonstrated high levels of C-reactive protein (CRP) in patients with AF compared to controls.<sup>32</sup> Furthermore, high CRP levels predict the recurrence of AF after electrical cardioversion.<sup>33</sup> Shin et al. studied 80 patients with atrial fibrillation (40 with persistent AF and 40 with paroxysmal AF) and compared them with 80 controls. Patients with AF had larger LA volumes and larger atrial "epicardial" fat volumes. Adiponectin, IL-6 and TNF- $\alpha$  levels were only measured in AF patients and not in controls. Patients with persistent AF had lower adiponectin levels and higher levels of IL-6 and TNF- $\alpha$  compared to patients with paroxysmal AF. The authors had carefully excluded patients with coronary artery disease.<sup>34</sup> The balance between the pro and anti-inflammatory actions of epicardial fat is not well understood. Whether a critical volume will tip the epicardial fat towards more pro-inflammatory role is unclear and needs to be studied.

### Epicardial fat and Atrial Fibrillation

Early studies focused on lipomatous hypertrophy of the interatrial septum and its association with



Table 1 : Prospective Trials of TEE Guided Cardioversion

Year	Authors	N	Imaging modality	Method	Main Findings
2006	Iacobellis et al	50	2 D Echo	Epicardial fat thickness over the Right ventricular free wall in parasternal long and parasternal short axis views	1- Obese patients had higher epicardial fat thickness compared to controls 2- Morbidly obese patients had larger LA and RA diameters and lower diastolic filling parameters 3- Epicardial fat thickness correlated with LA and RA diameters, even after correction for BMI
2009	Fox et al	997	8 slice MDCT	Pericardial fat measured as the fat tissue between the myocardium and pericardiac sac. Intrathoracic fat is the total fat in the thoracic cavity including the pericardial fat.	1- Using univariate analysis, pericardial fat, intrathoracic fat and visceral adipose tissue correlated with LV mass and left atrial dimensions In both genders. 2- After multivariate analysis, pericardial fat correlated with left atrial dimensions in men only
2010	Thanassoulis et al,	3217	8 slice MDCT	Measured pericardial fat volume as fat located between the myocardium and pericardiac sac. Measured intrathoracic fat as the fat within the thoracic cavity (including pericardial fat). Also measured abdominal fat	Pericardial fat volume is independently associated with prevalent AF, but not intrathoracic or visceral fat. Even after correcting for BMI and other clinical variables.
2010	Batal et al	169	64 slice MDCT	Measured periatrial fat thickness in three areas: with LA-ESO, LA-PA, LA-TA and also retrosternal fat	Only LA-ESO is associated with AF burden even after correction with other variables and doing a propensity score.
2010	Al Chek-akie et al.	300	64 slice MDCT	Pericardial fat volume is measured between the myocardium and the pericardial sac	1- Pericardial fat volume is larger in patients with persistent AF compared to patients with paroxysmal AF and sinus rhythm. 2- Pericardial fat volume correlated with measures of LA dimensions, as measured by 2 D Echocardiography and Cardiac CT 3-Pericardial fat was independently associated with AF, even after adjusting for other clinical variables and BMI
2011	Wong et al	130	MRI	Measured total pericardial fat (fat located between the myocardium and the parietal pericardium.	1-Pericardial fat is associated with the presence of AF, the severity of AF and left atrial volumes 2- Periatrial fat and periventricular fat volumes were also associated with AF burden and LA dimension. 3-Pericardial fat is associated with AF recurrence after AF ablation. These associations are both independent of and stronger than more systemic measures of adiposity.

2011	Tsao et al	102	64 slice MDCT	Total Periatrial pericardial fat volume (measured in atrial end diastole by tracing the pericardium from the pulmonary artery to the level of the coronary sinus) as well as volume in 8 areas surrounding the LA	1- periatrial pericardial fat volume was larger in patients with AF compared to controls. 2- Periatrial pericardial fat was unevenly distributed around the left atrium. 3- Total periatrial fat volume was independently associated with AF recurrence after ablation.
2011	Shin et al	160	64 MDCT	Total epicardial fat volume (measuring the fat between the myocardium and the pericardium). Also measured periatrial fat thickness and periventricular fat thickness	1-Total epicardial fat volume and periatrial fat thickness were larger in AF subjects compared to controls 2- Total epicardial fat volume and periatrial fat thickness were independently associated with LA remodeling. 3- Periventricular fat thickness was similar in patients with AF and controls.

atrial arrhythmias. Shirani et al. studied 80 patients with lipomatous hypertrophy of the interatrial septum. The thickness of the atrial septum correlated with the thickness of adipose tissue in the atrioventricular groove and 40% of these patients had atrial arrhythmias including atrial fibrillation while 67% of them had coronary artery disease.<sup>35</sup> Heyer et al. studied the multislice CT of 1292 patients who underwent CT imaging between 2001 and 2002 in his institution and found that lipomatous hypertrophy of the interatrial septum was found in 28 (2.2%) of patients. Of these 28 patients, 75% of them had increased "epicardial" fat and or intrathoracic fat while 61.9% had atrial arrhythmias including atrial fibrillation.<sup>36</sup> However, these two studies didn't measure the volume of the pericardial fat and were mostly retrospective in design. The association between visceral adipose tissue and left atrial dimensions was examined in several studies. Iacobellis et al. compared left atrial dimensions and measures of diastolic function in 30 patients with morbid obesity body mass index (BMI) > 40 kg/m<sup>2</sup> and 20 controls (normal BMI). Epicardial fat thickness was measured at the right ventricular free wall using 2 D Echo in parasternal short and parasternal long axis views. Obese patients had larger LA size, more impaired diastolic filling and higher epicardial fat thickness compared to controls.<sup>18</sup> Fox et al. studied 997 participants from the Framingham heart study using MDCT to quantify pericardial fat, intrathoracic fat and visceral adipose tissue and used MRI to quantify left ventricular mass, left ventricular end diastolic dimensions as well as left atrial dimensions. In both genders, pericardial

fat, intrathoracic fat and visceral adipose tissue correlated with LV mass and LA dimensions. But after correcting for other variables including BMI and visceral adipose tissue, pericardial fat was only correlated with LA dimensions in men.<sup>37</sup> This study did not focus on atrial fibrillation per se, but it is well known that left atrial dilatation is a risk marker for AF. The association between pericardial fat and left atrial dimensions raised interest in studying the association between pericardial fat and atrial fibrillation. Thanassoulis et al. studied 3217 patients in the Framingham Heart study who underwent MDCT between 2002 and 2005. Pericardial fat, intrathoracic fat and visceral adipose tissue volumes were calculated. Of these 3217 patients, only 54 (1.7%) had AF on electrocardiograms or holter monitors obtained prior to the MDCT study. After adjusting for other risk factors including age, gender and body mass index, only pericardial fat and not intrathoracic or abdominal visceral fat was independently associated with AF odds ratio (OR) for 1 standard deviation of volume 1.28, 95% Confidence interval (CI) 1.03-1.58, p=0.04.<sup>14</sup> This suggests that the local effects of pericardial fat are more associated with AF than the overall measures of obesity and was the first study to show an association between pericardial fat and AF. Two studies looked at pericardial fat and AF burden. Batal et al. studied 169 consecutive patients who underwent MDCT prior to AF ablation or for assessment of CAD. Epicardial fat thickness was measured in 3 areas near the left atrium: the first was between the LA and esophagus (LA-ESO), the second between the LA and thoracic

aorta (LA-TA) and the third area between the LA and pulmonary artery (LA-PA). Left atrial area was also measured in the 4-chamber view. Only epicardial fat thickness in the LA-ESO was independently associated with AF burden in patients with persistent AF (n=36), median of 56 mm, in patients with paroxysmal AF (n=60), median of 39 mm, and in patients without AF (n=73), median of 34 mm. After adjusting for other clinical variables including age, gender, BMI, LA area, hypertension, diabetes, coronary artery disease and congestive heart failure, LA-ESO thickness remained an independent predictor for AF burden (OR 6.17, 95% CI 1.60-23.85, p=0.008). The other two measures (LA-TA and LA-PA) didn't show such an association.<sup>19</sup> Whether the epicardial fat located near the posterior wall of the LA has a special role due to its proximity to all pulmonary veins or if it has different tissue characteristics is yet to be determined. This study measured periatrial fat thickness in predetermined areas and did not measure periatrial fat volume or total pericardial fat. Al Chekatie et al. studied 300 patients who underwent cardiac CT prior to AF ablation (n=218) or for evaluation for CAD (n=82). Patients with persistent AF have larger pericardial fat volumes  $101.6 \pm 44.1$  milliliters (ml) compared to patients with paroxysmal AF ( $93.9 \pm 39.1$  ml) and to patients in sinus rhythm ( $76.1 \pm 36.3$  ml).<sup>13</sup> And this association was independent of BMI and other traditional risk factors of atrial fibrillation. For each 10 ml increase in pericardial fat volume, there is a 13% increase in odds of developing AF (OR 1.13, 95% CI 1.03-1.24, p=0.01) after correcting for BMI and other clinical variables. Furthermore, there was also a correlation between pericardial fat volume and LA dimensions, measured as LA diameter by 2 D Echo (r=0.25, p=0.01), or LA volume using 2 D Echo (r=0.24, p=0.001) or LA volume measured by cardiac CT (r=0.36, p=0.001). The authors measured pericardial fat volume as a continuous variable and did not look at regional differences in pericardial fat (periatrial or periventricular fat). The work by Batal et al. and Al Chekatie et al. did not study the association between pericardial fat and ablation outcomes. Two other studies examined at the association between pericardial fat and ablation outcomes. Using cardiac MRI to quantify periatrial, periventricular and total pericardial fat, Wong et al. studied 102 patients undergoing catheter ablation for AF and 20 con-

trol patients without AF. Patients with AF had larger pericardial fat volumes (median  $299.9 \text{ cm}^3$ ) compared to patients in sinus rhythm (median  $168 \text{ cm}^3$ ). Patients with persistent AF had larger periatrial, periventricular and total pericardial fat volumes than patients with paroxysmal AF or controls.<sup>20</sup> Furthermore, total pericardial fat volume was also associated with LA volume (r=0.46, p<0.001) and ablation outcome, even after adjusting for BMI and LA dimensions (p=0.035 by log rank test). This association was independent of BMI, body surface area and LA size, suggesting that pericardial fat is more specific in identifying risk compared to general measures of obesity. This study was a single center study and was of small sample size, limiting the number of variables that they could adjust for in the model. Tsao et al. also studied the association between epicardial fat and ablation outcomes. They used MDCT to measure epicardial fat volume surrounding the atria and they also measured periatrial fat distribution in 8 areas around the left atrium. A total of 68 patients with AF (43 paroxysmal AF) and 34 controls were studied. Total epicardial fat volume surrounding the LA was significantly increased in AF patients compared to controls ( $35.2 \pm 12.5$  ml vs  $26.8 \pm 11.1$  ml respectively). The epicardial atrial fat was mostly located near the roof, near the left atrial appendage and lateral to the mitral isthmus and was significantly increased around the superior half of the LA compared to the inferior half of the LA ( $21.3 \pm 8.9$  ml vs  $14.2 \pm 5.0$  ml respectively, p < 0.001). Even after adjusting for other variables, including BMI, age, gender and LA volume and function, total epicardial fat surrounding the LA was independently associated with ablation outcome (p=0.04). There was no difference in epicardial fat volume surrounding the LA between patients with paroxysmal (n=43) and persistent AF (n=23), but this was a small sample size study. The distribution of epicardial fat was uneven in the LA, making the measurement of total volume a more accurate measure of periatrial epicardial fat.<sup>12</sup>

The only study of pericardial fat and AF to include markers of inflammation was the study by Shin et al. This study included 80 patients with AF (40 with Paroxysmal AF) and compared them with 80 controls. Total epicardial fat volume, periatrial and periventricular fat thickness were measured in all patients. Adiponectin, interleukin-6 and

high sensitivity CRP were measured in patients with AF only and not in controls. Compared to controls, patients with AF had larger left atrial volume, ( $125.4 \pm 41.6$  ml in AF pts vs  $73.3 \pm 19.5$  ml in control patients,  $p < 0.05$ ) total pericardial fat ( $83.8 \pm 26.8$  ml in AF patients vs  $67.2 \pm 23.1$  ml in controls,  $p < 0.05$ ) and thicker periatrial fat in the AV groove and in the interatrial septum, while periventricular fat thickness was not significantly different ( $4.0 \pm 1.2$  mm in AF patients vs  $3.7 \pm 1.2$  mm in controls). Furthermore, patients with persistent AF had larger total epicardial fat volume, thicker periatrial fat and lower adiponectin levels compared to patients with paroxysmal AF. Only total epicardial fat volume ( $p = 0.004$ ) and periatrial fat thickness in the interatrial septum ( $p = 0.016$ ) were independently associated with LA volume in patients with paroxysmal and persistent AF after adjusting for other clinical variables. This was the only study to include measures of inflammation and correlate it with AF burden and epicardial fat.<sup>34</sup> Table 1 summarized the above studies with the major findings. Currently, there is no known therapeutic intervention that affects the pericardial fat per se. Studies on posterior pericardiectomy in patients undergoing coronary artery bypass surgery focused on the incidence of post-operative pericardial effusion and atrial arrhythmias. Of these studies, two showed a significant decrease in the incidence of post-operative AF<sup>38,39</sup> and one failed to show similar results.<sup>40</sup> Statins have anti-inflammatory properties and have been shown to reduce the incidence of post-operative AF, but currently there is no study that focused on its effect on pericardial fat volume. The study by Mazurek et al. showed that the local inflammatory milieu didn't change with the presence of statins; however, this study was not randomized and was of small size and did not measure total pericardial fat volume.<sup>29</sup>

In animal models, starvation did not decrease epicardial fat thickness.<sup>21</sup> A study of 23 patients undergoing bariatric surgery showed that obese patients have higher epicardial fat thickness as measured by 2 D Echo compared to age and gender matched controls. Patients in this study had an average weight loss of  $40 \pm 14$  kilograms. Epicardial fat change after surgery ranged from a decrease of  $-5.3$  mm to an increase of  $1.3$  mm. Epicardial fat thickness decreased by an average of  $1$  mm in 11 patients (48%), and the degree of

change was only related to the baseline epicardial fat thickness ( $r = 0.71$ ,  $p < 0.001$ ). There was no relationship between the amount of weight lost and the change in epicardial fat thickness.<sup>41</sup> This study was of small size and measured epicardial fat thickness not volume.

## Conclusions

Epicardial fat is an active visceral adipose tissue and is associated with left atrial remodeling. Most of the epidemiological studies as well as the clinical studies have measured pericardial fat,<sup>13, 14</sup> which is the fat located within the fibrous pericardial sac. This can lead to overestimation of the epicardial fat volume, an important limitation of all imaging modalities.<sup>15</sup> The association between pericardial fat and AF is strong and well established; however, the exact mechanism(s) are not well defined. Pericardial fat volume and thickness were measured as continuous variables and there was no cut off proposed for upper normal limit in any of the above studies. There is currently no study giving a certain threshold where the balance between the pro and anti-inflammatory properties of pericardial fat is affected one way or the other. There is general agreement that total pericardial fat is associated with AF; however, a study showed that periventricular fat was associated with AF burden and ablation outcome,<sup>20</sup> and another study did not.<sup>12</sup> Whether periatrial fat plays a more important role than periventricular fat in AF, and whether atrial pericardial fat differs from periventricular fat in tissue characteristics is yet to be determined. More studies are needed to shed light on the effects of weight loss and other therapeutic interventions (including medications) on epicardial fat function, (especially its pro and anti-inflammatory properties) and volume.

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