Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice¹ and is associated with increased morbidity and mortality.² Although AF pathophysiology is complex, increasing evidence supports mechanistic links between inflammation and AF. AF has been associated with inflammatory conditions that involve the heart such as pericarditis and myocarditis.³,⁴ The incidence of AF after coronary artery bypass grafting is increased, with a peak duration and persistence.⁶–⁸ Higher levels of CRP predict pericarditis and myocarditis.³,⁴ The incidence of AF after inflammation plays a role in the pathogenesis of AF⁹–¹¹ further studies are necessary to examine cause and effect, and if inflammatory, paracrine mediators explain this association. (circ arrhythm electrophysiol. 2010;3:230-236.)

Key Words: atrial fibrillation • inflammation • obesity • pericardium • tomography

Experimental Section

Background—Atrial fibrillation (AF) has been linked to inflammatory factors and obesity. Epicardial fat is a source of several inflammatory mediators related to the development of coronary artery disease. We hypothesized that periatrial fat may have a similar role in the development of AF.

Methods and Results—Left atrium (LA) epicardial fat pad thickness was measured in consecutive cardiac CT angiograms performed for coronary artery disease or AF. Patients were grouped by AF burden: no (n 73), paroxysmal (n 60), or persistent (n 36) AF. In a short-axis view at the mid LA, periatrial epicardial fat thickness was measured at the esophagus (LA-ESO), main pulmonary artery, and thoracic aorta; retrosternal fat was measured in axial view (right coronary ostium level). LA area was determined in the 4-chamber view. LA-ESO fat was thicker in patients with persistent AF versus paroxysmal AF (P 0.011) or no AF (P 0.003). LA area was larger in patients with persistent AF than paroxysmal AF (P 0.004) or without AF (P 0.001). LA-ESO was a significant predictor of AF burden even after adjusting for age, body mass index, and LA area (odds ratio, 5.30; 95% confidence interval, 1.39 to 20.24; P 0.015). A propensity score–adjusted multivariable logistic regression that included age, sex, body mass index (BMI) (kg/m²), comorbidities included age, body mass index, LA area, and comorbidities was also performed and the relationship remained statistically significant (P 0.008).

Conclusions—Increased posterior LA fat thickness appears to be associated with AF burden independent of age, body mass index, or LA area. Further studies are necessary to examine cause and effect, and if inflammatory, paracrine mediators explain this association.
AF, and persistent AF). Paroxysmal AF was defined as recurring AF terminating in 7 days or less. Persistent AF indicated a history of AF sustaining beyond 7 days.

**Imaging Protocol**

Patients with known AF (n=95) were evaluated with cardiac CT angiography for PVI. Multidetector row CT technology was used (Definition, Siemens Medical Solutions, Erlangen, Germany, or Brilliance 64, Philips Medical Systems, Cleveland, Ohio). The specific imaging protocol for the clinically indicated scans was adapted to minimize radiation exposure for each patient while ensuring acceptable image quality. ECG-referenced scans were performed after intravenous administration of contrast material. Because pulmonary vein assessment was the primary clinical goal, 1.5-mm-thick images were reconstructed. Patients evaluated for CAD (n=74) were imaged using the same scanner models. Again, the specific imaging protocol was adapted for each patient and the ECG-referenced scan performed after the intravenous administration of contrast material. For evaluation of the coronary arteries, 0.75-mm-thick slices were reconstructed. For optimal visualization of coronary anatomy, patients were premedicated with sublingual nitroglycerin and intravenous β-adrenergic blocker for coronary dilatation and heart rate control, respectively.

**Image Analysis**

Using a standard clinical workstation (Leonardo, Siemens), advanced 3D off-line postprocessing was performed. The 3D CT dataset was reconstructed to obtain standard cardiac views as used in echocardiography. We first reconstructed standard 2- and 4-chamber views. LA size was determined by manually tracing the LA borders in the 4-chamber view (making sure to exclude the pulmonary veins) and using computer software that calculates the outlined area. The short-axis view was reconstructed as a plane perpendicular to the long axis of these 2 views at the level of the mid left atrium as indicated by the red line.

AF burden was analyzed by grade (no AF=0, paroxysmal=1, persistent=2). Continuous variables were compared using 1-way analysis of variance and were reported as mean±standard deviation if normally distributed, or they were compared using Kruskal-Wallis test and were reported as median±interquartile range if not normally distributed. Pearson χ² analysis was used to compare categorical variables. Bonferroni adjustment for multiple comparisons was applied after the overall 3 group comparisons.

**Statistical Methods**

Notes:

- Figures 1 and 2 were downloaded from http://circ.ahajournals.org on July 2, 2017.
Univariable and multivariable ordinal logistic regression models were constructed to test the association between periatrial LA-ESO fat thickness and AF burden. In the multivariable model, the covariates were age, BMI, and LA area. The proportional odds assumption was tested. Propensity scores were estimated by running logistic regression using the 75 percentile of LA-ESO as the response variable and age, BMI, LA area, and patient characteristics (sex, hypertension, hyperlipidemia, diabetes mellitus, CAD, congestive heart failure, and hypothyroidism) as the covariates. A propensity score–adjusted multivariable logistic regression was then performed to adjust for imbalances of the registry data.

Missing data of LA-ESO and BMI were imputed using overall mean imputation, and the imputed data were used to run logistic regressions as a supplement to the analyses of the original data. Statistical testing was 2-sided and results were considered statistically significant at the level of \( P \leq 0.05 \), or at \( P \leq 0.015 \) after Bonferroni correction. All analyses were conducted using SAS 9.1.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Patient characteristics of the entire study are summarized in Table 1. The mean age of the 169 patients included in this study was 54.6 ± 13.2 years (range, 15 to 82 years); 34.9% of patients were female. The mean BMI was 29.2 ± 6.1 kg/m². In this study population, 73 (43.2%) patients did not have AF, 60 (35.5%) had paroxysmal AF, and 36 (21.3%) had persistent AF. Comorbid conditions included CAD (15.4%), HTN (42.9%), HPL (41.6%), DM (7.1%), CHF (5.8%), CKD (1.9%), and thyroid disease (12.3%).

Characteristics by AF Burden

As shown in Table 1, patients without AF were younger than patients with paroxysmal AF (\( P = 0.001 \)) and persistent AF (\( P = 0.007 \)), respectively. The BMI of patients without AF (\( P = 0.311 \)) or with paroxysmal AF (\( P = 0.018 \)) and patients with persistent AF was not significantly different at the 0.015 significance level. The trend of a greater prevalence of CAD in patients without AF (versus paroxysmal AF \( P = 0.019 \); versus persistent AF \( P = 0.003 \)) probably reflected the initial indications for CT angiography. Patients specifically evaluated for CAD had a higher pretest probability of having CAD than patients who had the cardiac CT before PVI. Differences in other comorbid factors were not statistically significant.

Periatrial and RS Fat and LA Area Versus AF Burden

Periatrial and RS fat measurements by AF burden are summarized in Table 2. Patients with persistent AF had a significantly thicker LA-ESO fat pad as compared with patients with no AF (\( P = 0.003 \)) or with paroxysmal AF (\( P = 0.011 \)). A stepwise trend toward increasing LA-ESO thickness was observed in patients with increasing AF burden and is depicted in Figure 5.

The thickness of the RS fat pad at the level of the RCA takeoff was compared according to AF burden (Table 2). RS fat pad thickness was not associated with AF burden.

LA area was found to be larger in patients with persistent AF than in paroxysmal AF (\( P = 0.004 \)) or in patients without AF (\( P < 0.001 \)). This is shown in Table 2.

Regression Analysis

The association between AF burden by grade (no AF=1, paroxysmal=1, persistent=2) and periatrial LA-ESO fat
thickening was assessed by ordinal logistic regression. Univariately, LA-ESO was a significant predictor of AF burden (odds ratio, 5.30; 95% CI, 1.39 to 20.24; P=0.003). After adjusting for age, BMI, and LA area, the association remained significant (odds ratio, 6.06 [associated with a 1-cm increase in LA-ESO]; 95% CI, 1.90 to 19.25; P=0.002). After adjusting for age, BMI, and LA area, the association remained significant (odds ratio, 5.30; 95% CI, 1.39 to 20.24; P=0.015). The assumption of proportional odds was satisfied. Given that it was a registry study of imbalanced data, propensity scores were estimated in a logistic regression model by setting 75% percentile of LA-ESO as the outcome variable and age, BMI, LA area, and patient characteristics (sex, HTN, HPL, DM, CAD, CHF, and hypothyroidism) as the covariates. A propensity score–adjusted multivariable logistic regression was then performed. The obtained odds ratio was 6.17 (95% CI, 1.60 to 23.85; P=0.008).

To offset missing data of LA-ESO and BMI in the small sample size, overall mean imputation was applied to get a complete set of data. For adjusted ordinal logistic regression, with the overall mean imputation the odds ratio was 5.09 (95% CI, 1.51 to 17.19; P=0.009).

**Discussion**

In an imaging analysis of 169 patients with cardiac CT, we found a significant, direct, relationship between AF burden and the thickness of the posterior periatrial fat pad between the esophagus and the left atrium. Furthermore, this relationship remained statistically significant after adjusting for BMI, age, LA area, and propensity score.

AF has been associated with obesity, as well as elevated CRP levels, a measure of systemic inflammation. Left atrial biopsies from patients with lone AF have shown inflammatory cells. Obesity has been related to pericardial fat deposits. A similar relationship between obesity, epicardial fat, and inflammation has been described for CAD. It is increasingly recognized that distinct fat depots (such as subcutaneous and visceral fat deposits) differ in metabolic activity and in the proinflammatory mediators secreted. Epicardial adipose tissue is a form of visceral adipose tissue located between the myocardium and the parietal pericardium that shares a common embryonic origin with intraabdominal adiposity, a fat depot believed to play a role in metabolic syndrome. Epicardial fat is a source of several inflammatory mediators, including interleukin-1β, interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein-1. Paracrine interactions of these cytokines and mediators contribute to perivascular inflammation and the development of CAD. Because LA biopsies from

**Table 2. Left Atrial Size and Periatrial and Retrosternal Fat Thickness**

<table>
<thead>
<tr>
<th>Periatrial Fat Thickness (cm)</th>
<th>Total Population</th>
<th>No AF</th>
<th>Paroxysmal AF</th>
<th>Persistent AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA-PA, cm, median (IQR)</td>
<td>0.65 (0.44, 0.94) (n=157)</td>
<td>0.68 (0.44, 0.94) (n=68)</td>
<td>0.66 (0.45, 0.96) (n=56)</td>
<td>0.55 (0.41, 0.72) (n=33)</td>
</tr>
<tr>
<td>LA-ESO, cm, median (IQR)*</td>
<td>0.40 (0.25, 0.59) (n=139)</td>
<td>0.34 (0.21, 0.52) (n=56)</td>
<td>0.39 (0.27, 0.54) (n=55)</td>
<td>0.56 (0.40, 0.69) (n=28)</td>
</tr>
<tr>
<td>LA-TA, cm, median (IQR)</td>
<td>0.58 (0.39, 0.90) (n=148)</td>
<td>0.53 (0.39, 0.95) (n=62)</td>
<td>0.59 (0.41, 0.89) (n=55)</td>
<td>0.61 (0.39, 0.74) (n=31)</td>
</tr>
<tr>
<td>RS fat, cm, mean±SD</td>
<td>0.70±0.42 (n=164)</td>
<td>0.78±0.49 (n=72)</td>
<td>0.64±0.32 (n=57)</td>
<td>0.64±0.36 (n=35)</td>
</tr>
<tr>
<td>LA area, cm², mean±SD*</td>
<td>21.2±6.76 (n=169)</td>
<td>18.6±4.45 (n=73)</td>
<td>21.6±6.97 (n=60)</td>
<td>25.8±7.77 (n=36)</td>
</tr>
</tbody>
</table>

*P<0.015 when comparing LA-ESO in no AF versus persistent AF (P=0.003) and paroxysmal AF versus persistent AF (P=0.011) and LA area in no AF versus persistent AF (P<0.001) and paroxysmal AF versus persistent AF (P=0.004). All other comparisons, P>0.015. Bonferroni adjustment was applied in the multiple comparisons.
patients with AF have shown evidence of inflammatory cells in the atrial tissue and a local inflammatory response may have a role in the development of AF. We hypothesized that periatrial fat may be associated with AF, perhaps as a predictor of AF persistence or reflective of the inflammatory changes associated with AF.

It is interesting that only the LA-ESO (esophageal) periatrial fat was found to be associated with AF burden in our study. Triggers that contribute to the initiation of AF are located in the pulmonary vein ostia. The esophagus follows a course along the posterior wall of the left atria and is in close anatomic proximity to the pulmonary vein ostia. Local inflammatory mediators produced by the periatrial epicardial fat in the LA posterior wall may promote the activation of ectopic foci in the pulmonary vein ostia. Moreover, posterior pericardectomy during cardiac surgery has been associated with reduction in postoperative AF. This may in part be due to removal of the posterior esophageal pericardial fat pad.

Although epicardial adipose tissue is considered to be proinflammatory and is associated with metabolic syndrome and CAD, not all epicardial fat pads are similar. The heart is reported to have mainly 3 epicardial fat pads with parasympathetic ganglia: a fat pad on the anterior surface of the atria located between the inferior vena-cava and left atrium, and one between the superior vena-cava and right atrium. Reports about the impact of surgical preservation of the anterior fat pad between the aorta and right pulmonary artery on postoperative AF have had conflicting results. Epicardial fat pad ablation in canine models did not suppress AF inducibility in the long term. Nevertheless, in this study, only LA-ESO, which has not been characterized as having abundant parasympathetic ganglia, was significantly associated with AF. Of interest, the LA-TA, LA-PA, and RS fat pads were not associated with AF in our study population and rather appear to decrease in size with AF burden, but this did not achieve statistical significance. It is possible that in a larger study, the trend toward thicker nonposterior fat pads in the no AF group might reach statistical significance or correlate with the higher prevalence of CAD in the no AF group. CAD has been associated with epicardial fat, and the nonposterior fat pads probably are in closer proximity to the coronary arteries rather than the pulmonary veins.

Histological analysis and molecular identification of inflammatory markers may be necessary in future studies to better explain this association and to determine whether targeting left atrial adiposity is rational as a therapeutic goal. Preliminary data suggest a role for statins in the primary and secondary prevention of AF, possibly due to their anti-inflammatory effects. Although speculative, it is possible that patients with more posterior periatrial fat, such as patients with persistent AF, might derive more benefit from anti-inflammatory therapy to help reduce AF burden.

Limitations
The AF and no AF groups may not represent all patients with and without AF. AF patients in this study were younger than the typical AF population, which may lead to a lower prevalence of certain age-associated medical conditions such as HTN. This may limit the applicability of our results to all AF patients. Similarly, patients in the no AF group were generally referred for evaluation for CAD and thus had a larger prevalence of CAD and associated medical conditions. This may have contributed to the trend toward thicker nonposterior LA fat thicknesses observed in the no AF group, as previous literature suggests a relationship between coronary atherosclerotic disease and pericardial fat. Optimally, a matched control without AF and without CAD should be used; however, this would require a prospective enrollment of such patients in a controlled trial. Nonetheless, propensity score–adjusted logistic regression was performed to adjust for imbalances of the registry data.

Although blinding was potentially limited by differences in slice thickness and labeling for studies that assessed CAD, the CT reading was blinded to AF status. Although thickness of periatrial fat along the atrial wall is variable, the mid LA was used as a landmark to measure periatrial fat using the shortest distance to the esophagus, pulmonary artery, and thoracic aorta. A similar method was also applied to RS fat measurements, using the ostium of the RCA as the landmark.

Our method of quantifying fat has limitations as it is unclear if the epicardial fat thicknesses based on a short-axis view at the mid left atrium is representative of overall LA epicardial fat. A better assessment of periatrial and RS fat may have been possible if an automated method to measure the periatrial fat volume were available. Although such analytic approaches have been described to analyze epicardial fat surrounding the entire heart, we are currently unaware of software allowing limited assessment of periatrial fat burden. Future software development may allow future studies to include volumetric assessments of periatrial fat. Nevertheless, given the possible specific significance found in this study of LA-ESO fat, the posteriorly located fat pad located near the pulmonary veins where AF triggers are located, focal fat quantification may continue to be of interest, in addition to global periatrial fat volumes. Volumetric assessments may also overcome variability in posterior...
LA fat measurements may be related to dynamic changes in esophageal movement relative to the posterior LA wall.

Implications

In our study, we investigated whether or not LA epicardial fat is associated with atrial fibrillation. Our study suggests that the thickness of the posterior epicardial fat pad between the LA and the esophagus (LA-ESO), which can easily be measured using cardiac CT, is associated with an increased AF burden independent of the known AF risk factors of age, BMI, and LA size. This may be explained in part by its proximity to the pulmonary vein ostia, which have known contributions to AF pathogenesis. These findings have potential implications for better understanding of AF pathogenesis. Inflammation and inflammatory states have been not only associated with AF duration and persistence but also with the future development of AF in patients without prior history of AF. Although further studies are needed to determine the inflammatory role of the posterior LA epicardial fat pad and its cause-effect relationship with AF, measurement of LA-ESO thickness during cardiac CT may prove to have a similar role as other routinely measured inflammatory markers in relation to AF.

Conclusion

Increased posterior LA-ESO fat pad thickness appears to be associated with increased AF persistence, independent of age, BMI, and LA area. This first study to describe an association between LA pericardial fat and AF is hypothesis-generating but does not define causal connections. Future investigations are needed to further clarify the role of LA pericardial fat in AF and to study the potential inflammatory role of posterior pericardial adiposity at a microscopic and molecular level.

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Disclosures

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Inflammation plays a prominent role in cardiovascular disease and has been the focus of intense cardiovascular research. Furthermore, it is postulated to exert a locally toxic effect on coronary arteries via perivascular inflammation, therefore contributing to coronary atherosclerosis. In our study, we investigated whether or not left atrial epicardial fat may be associated with atrial fibrillation, given its proximity to the pulmonary veins ostia, which have known implications in atrial fibrillation (AF) pathogenesis. Our study suggests that the thickness of the posterior epicardial fat pad between the left atrium and the esophagus (LA-ESO), which can easily be measured using cardiac computed tomography (CT), is associated with an increased AF burden independent of the known AF risk factors of age, body mass index, and LA size. These findings have potential implications for better understanding of AF pathogenesis. Inflammation and inflammatory states have not only been associated with AF duration and persistence, but also with future development of AF in patients without prior history of AF. Further studies are needed to determine whether the epicardial fat in the posterior LA causes inflammation and subsequent AF or is merely associated with inflammation and AF. Measurement of LA-ESO thickness during cardiac CT may prove to have a role similar to other routinely measured inflammatory markers in relation to AF.
Left Atrial Epicardial Adiposity and Atrial Fibrillation
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