Relationships between left atrial pericardial fat and permanent atrial fibrillation: Results of a case-control study

D. Sevinc a,*, L. Pasaoglu b, R. Coskun c, N. Atci d, A. Alimli e

a Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Radiology, Yeni Bati Mah.2026 Cad. Batıkent Yenimahalle, Ankara, Turkey
b Ankara Numune Training and Research Hospital, Radiology, Ankara, Turkey
c Ankara Numune Training and Research Hospital, Cardiology, Ankara, Turkey
d Mustafa Kemal University, Medical Faculty, Department of Radiology, Radiology, Hatay, Turkey
e Gazi University, Medical Faculty, Department of Pediatric Radiology, Radiology Ankara, Turkey

KEYWORDS
Atrial fibrillation; Cardiac; Computed tomography; Pericardial fat

Abstract

Purpose: The goal of this study was to retrospectively investigate the relationships between pericardial fat, left atrium volume (LAV) as measured on multidetector row computed tomography (MDCT) and persistent atrial fibrillation (AF) using a case-control study.

Materials and methods: The study population consisted of 58 patients (19 men, 39 women; mean age, 67.8 ± 10 [SD] years) with persistent AF and 74 control subjects (30 men, 44 women; mean age, 67.8 ± 10.9 [SD] years). The associations between the presence of persistent AF and periatrial pericardial fat volume (PAFV), periatrial pericardial fat thickness (PAFT), and LAV as measured on MDCT were searched for using univariate and multiple linear regression analysis.

Results: On univariate analysis, significant differences were found between patients with AF and control subjects for mean PAFV (54.33 cm³ ± 23.43 [SD]; range: 12.2–111.1 cm³ vs 42.99 cm³ ± 20.76 [SD]; range: 7.4–103.9 cm³, respectively) (P=0.01), PAFT at the esophagus

Abbreviations: AF, Atrial fibrillation; LA, Left atrium; PAFV, Pericardial fat volume surrounding the LA; PAFT, Periatrial fat thickness; ECG, Electrocardiography; LA-ESO, The shortest fat thickness between the LA and the esophagus; LA-PA, The shortest fat thickness between the LA and the pulmonary artery; LA-DA, The shortest fat thickness between the LA and the descending aorta; BMI, Body mass index.

E-mail address: drderyasevinc@gmail.com (D. Sevinc).

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Atrial fibrillation (AF) is a common arrhythmia with high morbidity and mortality outcomes. AF frequency in the general population is 1% and its incidence rises with age [1–4]. The pathogenesis of AF is clearly multifactorial. AF is commonly accompanied by central obesity, hypertension, heart valve diseases, coronary artery diseases, heart failure and hyperthyroidism [4–6]. The pericardial fat is a special, metabolically active tissue with the same embryological origin as mesenteric and omental fat [7,8]. Pericardial fat affects the myocardium and coronary arteries by releasing many inflammatory mediators, leading to structural changes caused by inflammation [9,10]. Furthermore, mediators in pericardial fat may increase the predisposition to AF by increasing in vagal tonus through a direct local effect [10–12].

AF generally originates from the ectopic foci in the muscular sleeves reaching the pulmonary vein ostia in the left atrium (LA) [13]. It is believed that inflammation plays a significant role in AF etiopathogenesis [14]. Biopsies of the LA in patients with AF have shown a significant amount of inflammatory infiltrate in atrial tissue [1,15]. Inflammatory pathways may influence structural changes within LA and lead to the development of AF. Persistent AF is a chronic type of AF and several studies have reported the relationships between persistent AF and pericardial fat [16–20]. However, a relationship between the local pericardial fat deposits surrounding left atrium, persistent AF, and a potential effect of left atrium enlargement has not yet been evaluated clearly.

The goal of this study was to retrospectively investigate the relationships between pericardial fat, left atrial volume (LAV) as measured on multidetector row computed tomography (MDCT) and persistent AF using a case-control study.

Materials and methods

Study population

This prospective study was conducted between May 2012 and September 2012. Fifty-eight patients with persistent AF (19 men, 39 women) with a mean age of 67.8 years ± 10 (SD) (range, 48–90 years) were included. This group was compared to 74 age- and gender-matched controls without AF (30 men, 44 women) with a mean age of 67.8 years ± 10.9 (SD) (range, 34–86 years). The participants in this study were assessed by clinicians as having a low estimated likelihood of coronary artery disease. Coronary artery calcium scoring examination was performed to determine if additional cardiac testing was indicated. All participants fulfilled the inclusion criteria that consisted of atypical chest pain in combination with negative biomarkers and inconclusive electrocardiography. Exclusion criterion was having prosthetic heart valve that induced image artifacts.

The diagnosis of persistent AF was made when the patient had a type of arrhythmia lasting over one year, and when cardioversion has failed or not been tested. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or when the patient was receiving a treatment with an antihypertensive drug. Diabetes was defined as fasting plasma glucose level ≥ 126 mg/dL or treatment with insulin or a hypoglycemic drug. Clinically significant valvular disease was defined as a systolic murmur grade ≥ 3/6 or any diastolic murmur noted on examination by the clinic physician. Patients with heart failure and myocardial infarction event at any point before MDCT assessment were deemed to have heart failure or myocardial infarct, respectively. The local ethical committee approved the study, written informed consent for the research procedures was obtained.

Image acquisition and analysis

All participants underwent coronary artery calcium scoring evaluation using 16-slice MDCT scanner (Aquilion®, Toshiba Medical Systems Corporation, Otawara-shi, Japan). MDCT examinations were performed without intravenous administration of iodinated contrast material. No additional beta-blockers were given for heart rate control before the MDCT examination. The heart was scanned from the level of carina to the end of the left ventricular apex with 3-mm slice thickness and 300 mA, 120 kV, 0.25 ms scan time. In order to reduce stair-step artifacts caused by imaging in different cardiac cycle phases, data acquisition was performed using prospective ECG gating of the R–R interval. The obtained images were evaluated using a commercially available workstation (Vitrea, Minnetonka, MN, USA).
Periatrial fat measurement

First, two and four chamber views were obtained from the transverse images for pericardial fat thickness measurements. Afterwards, the short axis image was reconstructed perpendicular to the long axis of the two and four chamber images and passing through the middle of the LA (Fig. 1). Thickness measurements were performed from three different points of this image as follows:

- the shortest fat thickness between the LA and the esophagus (LA-ESO);
- the shortest fat thickness between the LA and the pulmonary artery (LA-PA);
- the shortest fat thickness between the LA and the descending aorta (LA-DA) (Fig. 1) [16].

Fat thickness was expressed in mm. Standard axes and accurate provided objective and reproducible measurements. The confidence of repeated measurements in a same patient was statistically proven. Afterwards the periatrial fat volume (PAFV) was measured and expressed in cm³. Fat voxels were identified using threshold attenuation values of −190 to −30 HU. On all of the transverse views the pericardium of the LA was manually drawn. The fat volume inside the pericardium surrounding the LA was measured on a workstation, using semiautomatic segmentation technique (Fig. 2). To determine the LA, the Simpson’s technique was used [21,22]. Characterizing the size of the LA according to its volume was preferred over a single linear dimension since enlargement can be different for different directions. LAV was calculated using summation of area × (slice thickness + interslice gap) for each slice. LA margins were manually drawn in all transverse sections. The LA appendage and the pulmonary veins were excluded at their junction with the LA on each image. LAV was measured on Workstation, using semiautomatic segmentation technique. Normalized LAV was calculated as the LAV divided by the body surface area (BSA) based on the Du Bois formula and expressed in cm³/m² [23]. Measurements were performed by a single investigator who was blinded to the clinical status of the patients. To determine the intra-observer reproducibility, one reader repeated measurements in 20 randomly selected patients.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc. Chicago, IL, USA). Whether the distributions of continuous variables were normally or not was determined by Kolmogorov Smirnov test. Quantitative data were expressed as mean ± SD or median and range, where applicable. While, the mean differences between groups were compared using Student t test, otherwise, Mann-Whitney U test was applied for comparisons of the median values. Qualitative data were analyzed using the Chi² test. Intra-observer and inter-observer reproducibility were assessed. Intraclass correlation coefficient (ICC) was used to evaluate the intra- and inter-observer variability.

The determination of the best predictor which may affect AF and LAV was evaluated by multiple logistic regression analysis after adjustment for all possible risk factors. Variables that were statistically significant among the groups in the univariate analysis were accepted as covariates in the multivariable model. Adjusted odds ratios and 95% confidence intervals (CI) were calculated for each variable. A P value < 0.05 was considered statistically significant.

Results

Although patients with AF and control subjects were matched for age, gender, comorbidities, and body mass index (BMI), there were significant differences with regard to LAV (Table 1).

Periatrial fat thickness (PAFT) and PAFV values are presented in Table 2. LA-ESO was significantly thicker in patients with AF than in control subjects (P < 0.001). LA-PA and LA-DA were not different between patients with AF and control subjects. PAFV was greater in AF patients than in control subjects (P = 0.01) (Table 2). The clinical and laboratory findings influencing normalized LAV are listed in Table 3. Univariate analysis showed that only PAFV was independently related to normalized LAV. Multiple logistic regression analysis revealed that only normalized LAV was an independent predictor of AF. Although PAFV and LA-ESO significantly associated with AF when based on univariate analysis, they were not independent risk factors on multivariate analysis (Table 4).

ICC value was 0.98 (95% CI, 0.95–0.99) for measurements of periatrial fat measurements and 0.99 (95% CI, 0.99–1.00) for LAV measurements. In a sample of 20 randomly selected patients, the ICC was 0.95 (95% CI, 0.92–0.97) for measurements of periatrial fat and 0.96 (95% CI, 0.96–0.99) for measurements of the LAV.

Discussion

In the present study, PAFV, LA-ESO and LAV were associated with persistent AF, based on the results of a univariate analysis. However, after adjustment for potential confounders,
only LAV was significantly associated with persistent AF. Moreover, there was a significant correlation between PAFV and normalized LAV in both AF subjects and the control group. These results suggest that pericardial fat might be associated with LA dilatation, which potentially could predispose to development of AF.

Recently, many studies have been conducted to investigate the relationship between pericardial fat and AF [16–20, 24–28]. In some of these studies, pericardial fat was defined as epicardial fat, and in others (including ours), it was expressed as a combination of both epicardial and pericardial fat. According to the results of all these studies, the relationships between AF and pericardial fat are complex and often contradictory. Several studies have demonstrated that patients with AF have a larger volume of pericardial fat compared with non-AF patients, which was especially evident in patients with persistent AF [16, 19, 20]. Recent studies have also shown that pericardial pericardial fat but not periventricular fat, is associated with AF [17, 18]. For instance, Wong et al. detected a significant correlation between pericardial fat volume and the presence and severity of AF on magnetic resonance imaging [18]. A few studies have investigated the effect of regional pericardial fat accumulation on AF [16, 24]. Recently, Batal et al. reported the potential local arrhythmogenic effect of the posterior pericardial fat pad on AF [16]. Though the potential relationship between pericardial fat and persistent AF identified in the current study is generally consistent with prior findings, there are two notable differences. Firstly, pericardial fat measurements did not significantly correlate with persistent AF after adjustment for confounders, including normalized LAV. Secondly, PAFV

Table 1 Clinical and demographic characteristics of 58 patients with persistent atrial fibrillation and 74 control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>AF patients</th>
<th>P value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>74 (56)</td>
<td>58 (44)</td>
<td>0.545</td>
<td>132 (100.0)</td>
</tr>
<tr>
<td>Age (years) (mean ± SD), [range]</td>
<td>[34–86]</td>
<td>[48–90]</td>
<td>0.360</td>
<td>62.9/37.1</td>
</tr>
<tr>
<td>Woman/Man (%)</td>
<td>67.2/32.8</td>
<td>67.8/32.2</td>
<td>0.197</td>
<td>27.47 ± 4.56</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean ± SD), [range]</td>
<td>[19.35–35.55]</td>
<td>[18.73–42.97]</td>
<td>0.297</td>
<td>1.81 ± 0.18</td>
</tr>
<tr>
<td>BSA (in m²) (mean ± SD), [range]</td>
<td>[1.36–2.04]</td>
<td>[1.40–2.29]</td>
<td>132 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities (n; %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (29.7)</td>
<td>16 (27.6)</td>
<td>0.788</td>
<td>38 (28.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51 (68.9)</td>
<td>47 (81.0)</td>
<td>0.116</td>
<td>98 (74.2)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40 (54.1)</td>
<td>25 (43.1)</td>
<td>0.213</td>
<td>65 (49.2)</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>6 (8.1)</td>
<td>9 (15.5)</td>
<td>0.185</td>
<td>15 (11.4)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (12.2)</td>
<td>12 (20.7)</td>
<td>0.185</td>
<td>21 (15.9)</td>
</tr>
<tr>
<td>Valvulopathy</td>
<td>20 (27.0)</td>
<td>23 (39.7)</td>
<td>0.126</td>
<td>43 (32.6)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>32 (43.2)</td>
<td>28 (48.3)</td>
<td>0.566</td>
<td>60 (45.5)</td>
</tr>
<tr>
<td>Normalized LA volume (cm³/m²) (mean ± SD), [range]</td>
<td>42.1 ± 25.43</td>
<td>78.3 ± 48.84</td>
<td>&lt; 0.001</td>
<td>56.1 ± 42.78</td>
</tr>
</tbody>
</table>

BMI: body mass index; LA: left atrium; BSA: body surface area. Normalized LA volume: the ratio of LA volume/BSA.
correlated well with LAV and LAV was significantly larger in AF patients.

LA size was an important confounder in the studies evaluating the relationship between AF and pericardial fat. Recently, in the Heinz Nixdorf Recall study, an analysis of 3467 participants demonstrated a significant correlation between pericardial fat and AF, but this effect was reduced or eliminated by further adjustment for LA size [28].

The relation between AF and atrial enlargement has been controversial for many years. Whether AF is the cause or the consequence of atrial enlargement has been a source of controversy for many years. LA remodeling and dilatation may result from a number of conditions that cause pressure or volume overload. Many conditions are associated with LA enlargement such as valvular heart diseases, heart failure and hypertension and these modulating factors can induce AF [29, 30]. Besides, there is convincing evidence demonstrating an important pathophysiological association between LA enlargement and AF [31–33]. Vaziri et al. reported that LA enlargement is an important precursor of AF and Tsang et al. showed that a larger LAV is associated with a higher AF risk in older patients [31, 32]. Similarly,
Osranek et al. revealed in a prospective study that LAV is a strong and independent predictor of post-operative AF [33].

Pericardial fat appeared to correlate well with LAV in some studies, suggesting a relationship between pericardial fat and LA remodeling [25]. Specifically, a large cohort study performed by Greif et al. [26] indicated that pericardial fat has been significantly associated with LA size, and Shin et al. [27] demonstrated that total and interatrial epicardial adipose tissues were independently associated with LAV in subjects with AF, as compared to a control group. Going beyond an observed connection between pericardial fat and LA size, researchers have also attempted to explain the mechanism by which pericardial fat affects LA dilatation. It has been suggested that the increased pericardial fat affects ventricular diastolic filling, causing atrial enlargement [34]. Additionally, diastolic dysfunction is known to be a strong predictor of LA remodeling and may contribute to electrical instability [35]. Recently, Iacobellis et al. showed that increased pericardial fat is associated with significantly impaired left ventricle diastolic function [36]. However, the pathogenic mechanism of these alterations is not yet well known, and more studies are needed to determine exact relationship. Our study supports the fact that increased pericardial fat is associated with structural alterations of the LA that could predispose the development of persistent AF. However, further researchs investigating the effect of pericardial fat on structural remodeling of LA are needed. Assessment of chest pain and coronary artery abnormalities is the most frequent application of cardiac MDCT [37]. However, results of our study indicate that the radiologists should pay attention to the pericardial fat.

The primary limitations of the current study are its relatively small number of participants and cross-sectional design. Another limitation is that we included only patients with persistent AF, so that a comparative assessment with other types of AF was not made. Our method of quantifying PAFV was a reproducible semi-automated method. However, PAFT was measured manually at the level of mid-LA. Since, the thickness of pericardial fat is variable along the atrial wall, a misestimation in quantification of PAFT may be noted. Measurement of obesity represents another limitation in our research, as the only systemic obesity indicator we used was BMI measurement. Finally, antropometric measurements of regional obesity, such as waist circumference and waist-to-hip ratio, were not included.

In conclusion, the results of our study reveal significant association between pericardial fat and persistent AF, which disappeared after adjustment for confounders. However, LAV was significantly associated with AF on multivariate analysis, and PAFV was significantly associated with LAV. The conflicting results of our study may be due to the small size and heterogeneity of the study population. Therefore, further studies are needed in order to determine the role of pericardial fat in AF pathophysiology.

Disclosure of interest

The authors declare that they have no competing interest.

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