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Pericardial fat volume is associated with clinical recurrence after catheter ablation for persistent atrial fibrillation, but not paroxysmal atrial fibrillation: An analysis of over 600-patients

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ABSTRACT

Background: Although pericardial fat volume (PFV) has been suggested to be associated with atrial fibrillation (AF), only a few studies have reported the association between pericardial fat and clinical outcome after radiofrequency catheter ablation (RFCA). The purpose of this study was to explore the factors associated with PFV and its prognostic significance after catheter ablation for AF, depending on the types of AF.
Methods: We included 665 patients (76.7% male, 57.3 ± 11.1 years of age, 67.7% with paroxysmal AF [PAF] and 32.3% with persistent AF [PeAF]) who underwent RFCA for AF, and compared PFV with clinical variables. The factors associated with clinical recurrence of AF were evaluated.
Results: 1. PFV (10 cm^3) was independently correlated with age (B = 0.09, 95% CI 0.06–0.13, $p < 0.001$), body mass index (BMI) (B = 0.25, 95% CI 0.12–0.38, $p < 0.001$), body surface area (BSA) (B = 10.51, 95% CI 7.64–13.39, $p < 0.001$), and left atrial (LA) dimension (B = 0.09, 95% CI 0.03–0.14, $p = 0.003$). 2. During the 19.3 ± 8.5 month follow-up period, the clinical recurrence rate was 26.5%. PFV (HR 1.06; 95% CI 1.02–1.10, $p = 0.004$) and PeAF (HR 1.86; 95% CI 1.31–2.62, $p < 0.001$) were independent predictors of clinical recurrence after RFCA. 3. PFV was significantly greater in PeAF patients with recurrence compared to those without ($p = 0.001$), but, not in the PAF group ($p = 0.212$). 4. PFV was independently associated with post-ablation recurrence only in PeAF (HR 1.10; 95% CI 1.05–1.16, $p < 0.001$).
Conclusions: PFV was independently associated with old age, greater LA dimension, and high BMI and BSA, and a significant predictor for AF recurrence after catheter ablation for PeAF.

1. Introduction

Atrial fibrillation (AF) is associated with obesity, metabolic syndrome, and inflammation [1–4]. Moreover, central obesity and visceral fat deposits other than systemic adiposity are stronger correlates of cardiovascular and metabolic risk factors [5,6]. Recently, several studies have demonstrated associations between pericardial fat and the presence of AF, severity of AF, and LA remodeling [7–11]. So far, however, only few studies with relatively small sample sizes have explored the association between pericardial fat and clinical outcome after radiofrequency catheter ablation (RFCA) for AF [9,12], and these results have not considered the types of AF. Since pericardial fat tissue is contiguous with the heart and has a shared blood supply with the myocardium and coronary arteries, local paracrine and inflammatory effects via secretion of inflammatory adipokines are assumed to play critical roles in the pathogenesis of AF [13,14]. So, most studies have indicated that inflammation could be the major mechanism of pericardial fat responsible for AF. However, multiple mechanisms contribute to the pathophysiology of AF, and the inflammation and metabolic risk factors play some role with varied degrees depending on the types of AF [15,16]. Therefore, we hypothesized that pericardial fat volume (PFV) may affect clinical outcome after RFCA of AF mainly via inflammatory process and has the difference in clinical recurrence according to the types of AF. The purpose of this study was: 1) to explore PFV associated clinical factors, 2) to characterize the predictive value of PFV with clinical outcome after catheter ablation for AF, and 3) to investigate the different effects of PFV in patients with paroxysmal AF (PAF) and persistent AF (PeAF).

Abbreviations: AF, atrial fibrillation; AAD, anti arrhythmic drug; BMI, body mass index; BSA, body surface area; CFAE, complex fractionated atrial electrogram; CPVI, circumferential pulmonary vein isolation; LA, left atrium; LV, left ventricle; LVEDD, LV end diastolic dimension; LVEF, LV ejection fraction; LVMI, LV mass index; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PFV, pericardial fat volume; PV, pulmonary vein; RFCA, radiofrequency catheter ablation; TIA, transient ischemic attack.

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2. Methods

2.1. Study population

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at the Yonsei University Health System. All

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patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database. This study included 665 consecutive patients with AF (76.7% male, 57.3 ± 11.1 years old) who underwent RFCA, and the mean duration of AF was 3.8 ± 3.1 years. Among them, 450 (67.7%) patients had PAF and 215 (32.3%) had PeAF. The study's exclusion criteria were as follows: 1) permanent AF refractory to electrical cardioversion, 2) AF with valvular disease ≥grade 2, 3) associated structural heart disease other than left ventricular hypertrophy, 4) history of prior RFCA or cardiac surgery, and 5) the patients whose 3D-cardiac CT image were not acceptable for PFV analysis. Before the ablation, the absence of a left atrial (LA) thrombus was confirmed by transesophageal echocardiography. To define the anatomy of pulmonary vein (PV) and left atrium (LA), 3D-cardiac CT images were acquired in all patients. All antiarrhythmic drugs were discontinued for a minimum period of five half-lives and amiodarone was stopped at least 4 weeks before the procedure.

2.2. PFV measurement

CT scans were performed within a week before RFCA (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Netherlands). Pericardial fat was defined as the adipose tissue within the pericardial sac, and the CT attenuation threshold for fat detection was between −190 and −30 Hounsfield units (HU) as used in previous studies [7,8]. Two independent investigators who were blinded to the patients' clinical information quantified pericardial fat using computer software (ITK-SNAP, Penn Image Computing and Science Laboratory (PICSL), University of Pennsylvania, USA) [17]. First, axial CT images (0.5 to 0.75 mm slice thickness) from the superior border of the pulmonary trunk bifurcation through the apex of the left ventricle inferiorly were obtained. Next, the investigator placed the 10 to 15 control points on the pericardium in every 10 mm transverse view [10,18]. Then, from these control points, a 3D active tool was initiated to achieve automatically generated contouring of the pericardial margin along the pericardial fat voxels. After this semiautomatic segmentation, the pericardial fat volume was automatically interpolated. Additionally, a manual adjustment was performed using a paintbrush tool, if deemed appropriate (Fig. 1A). The correlation coefficients for inter-observer and intra-observer reliability were 0.96 and 0.97, respectively ($p < 0.001$).

2.3. Electrophysiologic mapping and radiofrequency catheter ablation

Details regarding electrophysiologic mapping and RFCA technique and strategy were as described in previous studies [19,20]. In brief, we used an open irrigated-tip catheter (Celsius, Johnson & Johnson Inc.; Diamond Bar, CA, USA; Coolflex, St. Jude Medical Inc., Minnetonka, MN, USA; 30–35 W; 47 °C) to deliver RF energy for ablation. All patients initially underwent circumferential pulmonary vein isolation (CPVI) and bi-directional block of the cavo-tricuspid isthmus. For the patients with PeAF, we added a roof line, posterior inferior line, and anterior line [21] as the standard lesion set. The operator could opt to perform additional ablations in the superior vena cava or non-PV foci, or conduct complex fractionated electrograms [22] at his discretion. The procedure was complete when there was no immediate recurrence of AF after cardioversion with isoproterenol infusion (5 μg/min). If there were mappable AF triggers or atrial premature beats, we carefully mapped and ablated those non-PV foci as much as possible. All RFCA procedures were conducted according to the above specific protocol by 2 operators with over 10 years of experience.

2.4. Follow-up after ablation

All patients were followed with anti-arrhythmic drugs discontinued after RFCA. Patients were asked to attend scheduled outpatient follow-up appointments 1, 3, 6, 9, and 12 months after RFCA and every 6 months thereafter. An electrocardiogram (ECG) was obtained at every visit and additional ECGs were performed when patients' symptoms were suggestive of AF. A 24- to 48-h Holter ECG monitor or an event recorder was worn at 3, 6, 12, 18, and 24 months at a minimum according to the 2012 HRS/EHRA/ECAS Expert Consensus Statement guidelines [23]. Additionally, whenever patients reported symptoms of palpitations, Holter monitor or event monitor recordings were obtained and evaluated for possible recurrence of the arrhythmia. We defined recurrence of AF as any episode of AF or atrial tachycardia lasting longer than 30 s. Any ECG documentation of AF recurrence after 3 months was diagnosed as clinical recurrence.

2.5. Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows (version 20.0). Continuous variables were expressed as the mean ± standard deviation (SD) and compared by students' *t*-tests and ANOVAs. Categorical variables were reported as frequencies (percentage) and compared by Chi-square tests or Fisher's exact tests. Multivariate linear regression analysis was used to identify predictors of PFV. Kaplan–Meier analysis with log-rank test was used to calculate AF recurrence free survival over time, and to compare recurrence rates across groups. Multivariate Cox regression analysis was used to assess the independent predictors for AF recurrence after RFCA. A p-value < 0.05 (two-sided) was considered to be statistically significant.

3. Results

3.1. High PFV in elderly patients with high body mass index (BMI) and greater LA dimension

Table 1 shows baseline characteristics of overall study population and with respect to the presence or absence of clinical recurrence. Table 2 summarizes the linear regression analysis for clinical variables associated with PFV (10 cm^3). Old age (B = 0.09, 95% confidence interval [CI] 0.06–0.13, $p < 0.001$), high BMI (B = 0.25, 95% CI 0.12–0.38, $p < 0.001$), high body surface area (BSA) (B = 10.51, 95% CI 7.64–13.39, $p < 0.001$), and greater LA dimension (B = 0.09, 95% CI 0.03–0.14, $p = 0.003$) were independently associated with PFV.

3.2. High PFV and PeAF are predictors for poor clinical outcome after AF ablation

During the mean follow-up period of 19.3 ± 8.5 months, 176 participants out of 665 patients (26.5%) experienced clinical recurrence of

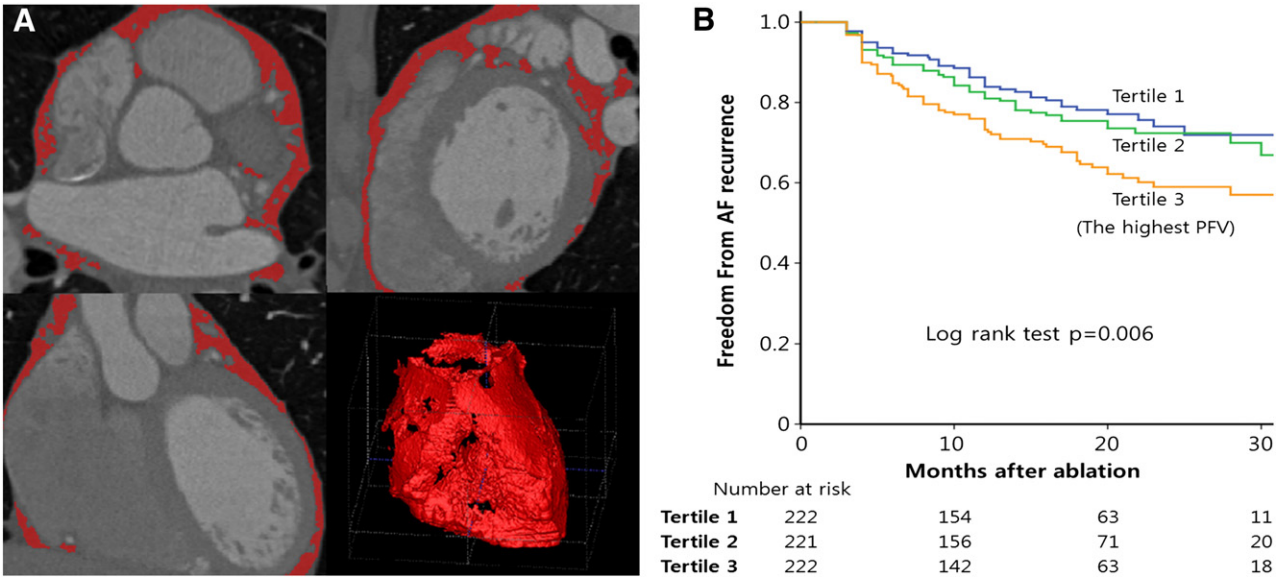

Fig. 1. A. Measurement of PFV by 3D CT. PFV was measured on axial (left upper panel), sagittal (right upper panel), and coronal (left lower panel) CT images by semi-automatic segmentation, and quantified using 3-D reconstructed images with automatic interpolation (right lower panel) via computer software. B. Kaplan–Meier analysis for AF-free survival after the catheter ablation.