

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

Tae-Hoon Kim

Department of Medicine

The Graduate School, Yonsei University

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An analysis of over 600-patients

Directed by Professor Hui-Nam Pak

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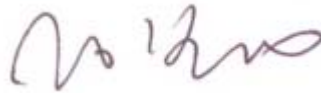
Tae-Hoon Kim

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This certifies that the Master's Thesis of
Tae-Hoon Kim is approved.



Thesis Supervisor : Hui-Nam Pak



Thesis Committee Member#1 : Boyoung Joung



Thesis Committee Member#2 : Hyuk-Jae Chang

The Graduate School
Yonsei University

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ABSTRACT

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

Tae-Hoon Kim

*Department of Medicine
The Graduate School, Yonsei University*

(Directed by Professor Hui-Nam Pak)

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 the prognostic significance of PFV 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. On linear regression analysis, PFV (10cm^3) was independently correlated with male gender ($B=2.38$, 95% CI 1.65-3.12, $p<0.001$), body mass index ($B=0.59$, 95% CI 0.48~0.69, $p<0.001$), and age ($B=0.07$, 95% CI 0.04~0.10, $p<0.001$). 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 male gender, high body mass index, and old age, and a significant predictor for clinical recurrence of AF after catheter ablation for PeAF.

Key words : *atrial fibrillation, pericardial fat, recurrence, catheter ablation*

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I. 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.⁷⁻¹⁰ 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,^{9,11} but 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.^{12,13} 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.^{14,15} Therefore, we hypothesized that pericardial fat volume (PFV) may affect clinical outcome after RFCA of AF mainly via inflammatory process and may have 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).

II. MATERIALS AND METHODS

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 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. 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 \geq 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 images 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.

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 (PICS), University of Pennsylvania, USA).¹⁶ 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.^{10,17} 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 (Figure 1A). The correlation coefficients for inter-observer and intra-observer reliability were 0.96 and 0.97, respectively (p<0.001).

Electrophysiologic mapping and radiofrequency catheter ablation

Details regarding electrophysiologic mapping and RFCA technique and strategy were as described in previous studies.^{18,19} 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 line²⁰ 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 electrograms²¹ at his discretion. The procedure was complete when there was no immediate recurrence of AF after cardioversion with isoproterenol infusion (5µg/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.

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-hour 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.²² 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 sec. Any ECG documentation of AF recurrence after 3 months was diagnosed as clinical recurrence.

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 \pm standard deviation (SD) and compared by student's *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.

III. RESULTS

High PFV in elderly male patients with high BMI

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 (10cm^3). Old age (B=0.07, 95% Confidence Interval [CI] 0.04~0.10, $p<0.001$), male gender (B=2.38, 95% CI 1.65~3.12, $p<0.001$), and high body mass index (B=0.59, 95% CI 0.48~0.69, $p<0.001$) were independently associated with PFV in multi-variate linear regression analysis.

Table 1. Comparison of AF patients according to clinical recurrence.

	Overall (n=665)	Clinical recurrence (n=176)	No recurrence (n=489)	<i>p</i> -value
Male (%)	510 (76.7%)	141 (80.1%)	369 (75.5%)	0.211
Age (years)	57.3 ± 11.1	58.1 ± 10.7	56.9 ± 11.2	0.233
PeAF (%)	215 (32.3%)	82 (46.6%)	133 (27.2%)	<0.001
BSA (m ²)	1.81±0.17	1.82±0.17	1.81±0.17	0.462
BMI (kg/m ²)	24.71±3.05	24.66±2.91	24.72±3.10	0.829
CHADS ₂ score	0.88±1.02	0.87±0.99	0.88±1.03	0.929
Heart failure (%)	22 (3.3%)	4 (2.3%)	18 (3.7%)	0.370
Hypertension (%)	309 (46.5%)	79 (44.9%)	230 (47.0%)	0.624
Age >75 yrs (%)	25 (3.8%)	6 (3.4%)	19 (3.9%)	0.776
Diabetes (%)	87 (13.1%)	25 (14.2%)	62 (12.7%)	0.607
Stroke/TIA (%)	70 (10.5%)	20 (11.4%)	50 (10.2%)	0.673
LA diameter (mm)	41.53±6.24	42.42±6.39	41.21±6.16	0.027
LAVI (ml/m ²)	34.72±12.27	36.70±12.48	34.01±12.12	0.015
LVEDD(mm)	49.79±4.29	49.58±3.85	49.87±4.44	0.452
LVEF (%)	63.29±8.33	63.06±7.17	63.38±8.72	0.664
LVMI (g/m ²)	94.10±21.58	94.73±24.26	93.88±20.61	0.694
PFV(cm ³)	103.08±44.44	113.19±48.11	99.44±42.51	<0.001
Early recurrence	205 (30.8%)	97 (55.1%)	108 (22.1%)	<0.001

Values are expressed in n (%) or mean±SD.

AF: atrial fibrillation, PeAF: persistent atrial fibrillation, BSA: body surface area, BMI:

body mass index, TIA: transient ischemic attack, AAD: anti arrhythmic drug, LA: left atrium, LAVI : LA volume index, LV: left ventricle, LVEDD: LV end diastolic dimension, LVEF: LV ejection fraction, LVMI: LV mass index, PFV: pericardial fat volume.

Table 2. Linear regression analysis for clinical variables predictive of PFV (10 cm³).

PFV (10 cm ³)	Univariate analysis		Multivariate analysis	
	B (95% CI)	p-value	B (95% CI)	p-value
Male	2.36 (1.58 – 3.14)	<0.001	2.38 (1.65 – 3.12)	<0.001
Age	0.04 (0.01 – 0.07)	0.006	0.07 (0.04 – 0.10)	<0.001
PeAF	0.75 (0.02 – 1.47)	0.043	0.13 (-0.52 – 0.78)	0.694
BMI, kg/m ²	0.58 (0.48 – 0.68)	<0.001	0.59 (0.48 – 0.69)	<0.001
Hypertension	0.95 (0.28 – 1.62)	0.005	0.01 (-0.65 – 0.67)	0.971
Diabetes	1.35 (0.36 – 2.34)	0.008	0.17 (-0.77 – 1.12)	0.719
LVEDD (mm)	0.12 (0.04 – 0.19)	0.004	0.00 (-0.78 – 0.70)	0.911
LA volume index (ml/m ²)	0.01 (-0.02 – 0.04)	0.399		

PFV: pericardial fat volume, PeAF : persistent atrial fibrillation, BMI: body mass index, LV: left ventricle, LVEDD: LV end diastolic dimension, LA: left atrium, LAVI : LA volume index.

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 AF. Patients with clinical recurrence were more likely to have PeAF (p<0.001), greater LA diameter (p=0.027), LA volume index (p=0.015), or PFV (p<0.001), and a higher early recurrence rate (p<0.001) than those who remained in sinus rhythm (n=489, Table 1). The Kaplan-Meier analysis of tertiles of PFV showed a significantly higher clinical recurrence rate in the highest tertile PFV group compared with the other groups (Log-rank test p=0.006, Figure 1B). On the multi-variate Cox regression analysis, PeAF (HR 1.86; 95% CI 1.31~2.62, p<0.001) and PFV (10cm³, HR 1.06; 95% CI 1.02~1.10, p=0.004) and were independently associated with clinical recurrence of AF after catheter ablation (Table 3).

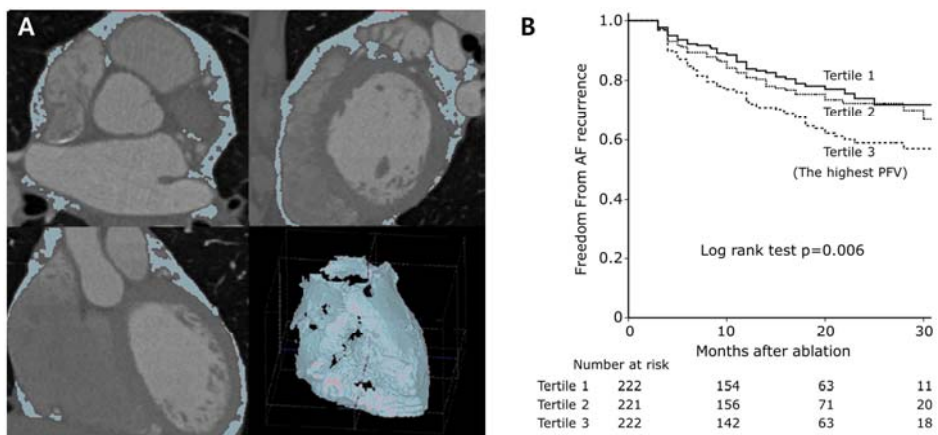


Figure 1. A. Measurement of PFV by 3D CT. PFV was measured on axial (left

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.

Table 3. Univariate and multivariate Cox regression analysis for the clinical recurrence of AF.

Total AF population	Univariate analysis		Multivariate Model*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male	1.26 (0.87 – 1.82)	0.223		
Age	1.01 (0.99 – 1.02)	0.226		
PeAF	1.99 (1.48 – 2.68)	<0.001	1.86(1.31 – 2.62)	<0.001
LA volume index (ml/m ²)	1.01 (1.00 – 1.03)	0.021	1.00 (0.99 – 1.02)	0.518
PFV, 10cm ³	1.05 (1.02 – 1.09)	0.001	1.06 (1.02 – 1.10)	0.004
Hypertension	0.92 (0.68 – 1.23)	0.561		
Diabetes	1.17 (0.76 – 1.78)	0.478		
BMI	0.99 (0.94 – 1.04)	0.676		

* additionally age, sex and BMI adjusted.

AF: atrial fibrillation, PeAF: persistent atrial fibrillation, BMI: body mass index, LA: left atrium, PFV: pericardial fat volume, HR: Hazard Ratio, CI: confidence interval

PFV is an independently associated with AF recurrence after PeAF ablation

PFV was greater in PeAF patients than in PAF patients (108.13±46.88

vs. 100.67 ± 43.07 , $p=0.043$). While PFV was significantly greater in PeAF patients with recurrence than in those without ($p=0.001$), there was no such difference in PAF group ($p=0.212$, Figure 2). With consistence, Kaplan-Meier analysis showed that the highest tertile PFV group had a significantly higher clinical recurrence rate among the patients with PeAF (Log-rank test $p=0.029$, Figure 3A). However, there was no such difference of clinical recurrence rates depending on PFV in PAF patients ($p=0.470$, Figure 3B). Multi-variate Cox regression analysis revealed that PFV (10cm^3 , HR 1.09; 95% CI 1.04~1.14, $p<0.001$) was independently associated with clinical recurrence of AF after catheter ablation in PeAF after age, sex and BMI adjustment. However, PFV (10cm^3 , HR 1.02; 95% CI 0.98 - 1.07, $p=0.378$) was not associated with post-RFCA recurrence after PAF ablation (Table 4).

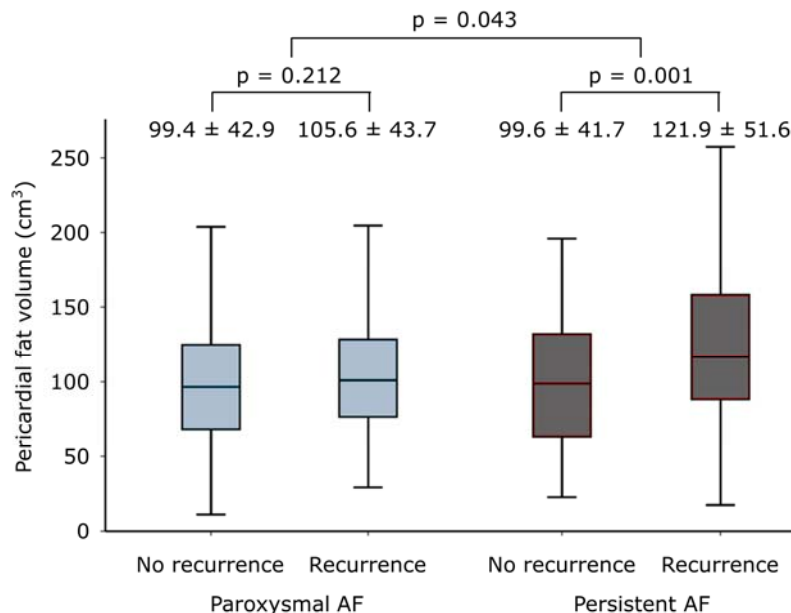


Figure 2. Comparison of PFV between patients with PeAF and PAF.

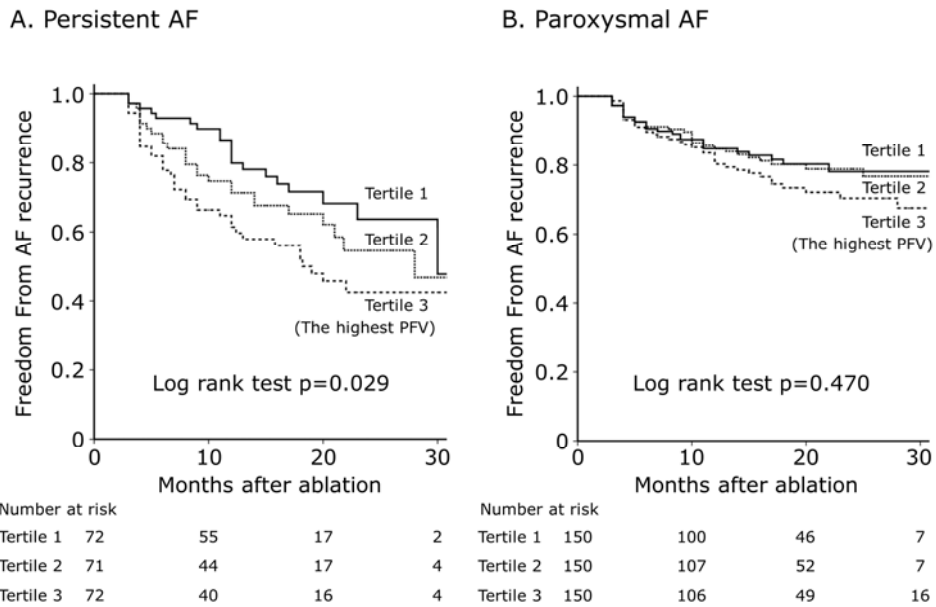


Figure 3. Kaplan-Meier analyses for AF-free survival after the catheter ablation in patients with PeAF (A) and PAF (B)

Table 4. Cox regression analysis for the clinical recurrence according to the type of AF..

PeAF	Univariate analysis		Multivariate model*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male	1.10 (0.61 – 1.99)	0.754		
Age	1.01 (0.99 – 1.03)	0.500		
LA volume index (ml/m ²)	1.00 (0.99 – 1.02)	0.746		
PFV, 10cm ³	1.09 (1.04 – 1.14)	<0.001	1.10 (1.05 – 1.16)	<0.001
Hypertension	0.71 (0.46 – 1.10)	0.122		

Diabetes	0.99 (0.56 – 1.77)	0.985		
BMI	0.99 (0.92 – 1.05)	0.649		
PAF	HR (95% CI)	p-value	HR (95% CI)	p-value
Male	1.18 (0.73 – 1.91)	0.492		
Age	1.01 (0.99 – 1.03)	0.340		
LA volume index (ml/m ²)	1.00 (0.99 – 1.02)	0.656		
PFV, 10cm ³	1.02 (0.98 – 1.07)	0.378		
Hypertension	1.06 (0.71 – 1.60)	0.766		
Diabetes	1.16 (0.62 – 2.17)	0.653		
BMI	0.97 (0.90 – 1.05)	0.973		

* additionally age, sex and BMI adjusted.

AF: atrial fibrillation, PeAF: persistent atrial fibrillation, BMI: body mass index, LA: left atrium, PFV: pericardial fat volume, HR: Hazard Ratio, CI: confidence interval.

IV. DISCUSSION

In the current study, we explored the clinical and prognostic implications of PFV in over 600 patients with AF who underwent catheter ablation. We found that PFV was independently associated with old age, male gender, and high body mass index. High PFV predicted poor clinical outcome after catheter ablation consistent to the previous small volume studies, but this prognostic value of PFV was found in patients with PeAF, but not in those with PAF.

Potential roles of pericardial fat in the pathogenesis of AF

Recently, several studies have shown an association between PFV, cardiovascular disease, and AF.^{5-9,23,24} Local inflammatory responses in pericardial fat were thought to play an important role in the genesis of AF and electroanatomical remodeling of the LA. Pericardial fat tissue also contains an abundance of ganglionate plexi, which influence on cardiac autonomic nerve activity related to local inflammation.²⁵ Furthermore, PFV reflects visceral fat deposits rather than systemic adiposity,⁵ so that pericardial fat is associated with cardiovascular disease, hypertension,²⁶ diabetes mellitus,²⁷ dyslipidemia,²⁸⁻³⁰ and metabolic aspects of AF. Therefore, PFV may provide a complex and multifactorial inflammatory mechanism that contributes to the development of AF and post-RFCA recurrence.

Clinical implication of PFV in AF catheter ablation

Although there have been a few reports with a small sample size regarding to high recurrence of AF after catheter ablation in patients with high PFV,^{9,11} these studies did not consider the types of AF. In the current study, we included over 600 patients and found consistent prognostic value of PFV after AF catheter ablation in patients with PeAF. But, that was not the case in patients with PAF. Several authors have reported that the volume of pericardial fat is higher in PeAF than in PAF.^{8,10,11} However, this relationship between PFV and type of AF was not statistically significant in this study, even though both PeAF

and high PFV were independently associated with higher recurrence rate of AF after RFCA. Then, what is the mechanism of high PFV contributing to PeAF recurrence? First, the major mechanism responsible for recurrence of PeAF is associated with inflammation,³¹ atrial substrate,¹⁹ non-PV foci,³² or autonomic nerves.³³ In contrast, CPVI is good enough for patients with PAF,³⁴ because major mechanism of PAF is associated with PV triggers.^{32,35} Therefore, pericardial fat associated pro-inflammatory or autonomic effects cannot be treated efficiently by RFCA of endocardial approach, especially in PeAF patients with thick pericardial fat. Additional anti-inflammatory drugs, such as steroids may be helpful for this specific patient group.³¹ Second, AF is a chronic degenerative disease associated with metabolic effects and ageing. Mohanty et al. recently have suggested that the presence of metabolic syndrome and baseline inflammatory markers predicted higher recurrence after RFCA only in patients with non-paroxysmal AF.¹⁵ Therefore, continuous metabolic and inflammatory change of atrial substrate may contribute to the recurrence or new development of AF in patients with PeAF, while PV reconnection might be a main mechanism of AF recurrence in patients with PAF.

Study limitations

Since this is a single center cohort study that included a selective group of patients referred for AF catheter ablation, findings cannot be generalized to all types of AF within the general population. It remains unclear whether the

clinical significance of PFV has a cause-and-effect relationship with AF recurrence, or whether the two are simply associated.

V. CONCLUSION

PFV was an independent predictor for AF recurrence after catheter ablation, and was associated with male gender, high body mass index, and old age. PFV was associated with clinical recurrence of AF in PeAF patients, whereas not in the patients with PAF. Because PFV and local inflammation seem to be associated with the pathogenesis and recurrence of AF in PeAF patients, PFV could be a useful marker for predicting recurrence after RFCA in patients with PeAF and with high volume of pericardial fat.

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ABSTRACT(IN KOREAN)

심막지방이 심방세동 전극도자 절제술의 임상적 결과에 미치는
영향

<지도교수 박희남>

연세대학교 대학원 의학과

김태훈

심막지방과 심방세동의 연관성은 이미 알려져 있으나 심막지방과 전극도자 절제술을 받은 심방세동 환자에서의 심방세동 재발과의 연관성에 대한 보고는 거의 없는 실정이다. 따라서 본 연구는 심막지방의 양과 관련인자, 전극도자 절제술 후의 예후를 심방세동의 종류에 따라 확인하고자 하였다.

665명 (남자 76.7%, 평균나이 57.3 ± 11.1세, 발작성 심방세동 67.7%, 지속성 심방세동 32.3%) 의 전극도자 절제술을 시행 받은 심방세동 환자를 대상으로 하였으며, 심막지방의 특성과 전극도자 절제술 후 임상 재발의 예측인자를 조사하고 심방세동의 종류 (발작성, 지속성)에 따른 차이를 분석하였다.

심막지방의 부피는 성별 (남성, B=2.38, 95% CI 1.65-3.12, p<0.001), 체질량지수 (body mass index) (B=0.59, 95% CI 0.48~0.69, p<0.001), 그리고 연령 (B=0.07, 95% CI 0.04~0.10, p<0.001) 과 독립적인 연관성을 가졌다. 19.3 ± 8.5 개월 간의 추적 관찰 기간 동안 임상재발률은 26.5%

이었으며, 심막지방의 부피 (HR 1.06; 95% CI 1.02~1.10, $p=0.004$) 와 지속성 심방세동 (HR 1.86; 95%CI 1.31~ 2.62, $p<0.001$) 이 전극도자 절제술 후 임상재발의 독립적인 예측인자로 확인되었다.

심막지방은 지속성 심방세동 환자 중 임상재발을 보인 환자가 재발을 보이지 않은 환자에 비해 그 부피가 더 큰 것으로 확인되었으나 ($p=0.001$), 발작성 심방세동 환자에서는 이런 경향을 보이지 않았다 ($p=0.212$). 심막지방은 오로지 지속성 심방세동 환자에 있어서만 전극도자 절제술 후 임상재발과 독립적인 상관관계를 보였다 (HR 1.10; 95%CI 1.05~1.16, $p<0.001$).

결론적으로, 심막지방은 남성, 높은 체질량지수, 고령의 환자에 있어서 더 큰 부피를 가지며, 발작성 심방세동이 아닌 지속성 심방세동의 전극도자 절제술 후 임상재발의 유의한 예측인자로 생각된다.

핵심되는 말 : 심방세동, 심막지방, 재발, 전극도자 절제술