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Original Article

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Left Atrial Dysfunction, Fibrosis and the Risk of Thromboembolism in Patients With Paroxysmal and Persistent Atrial Fibrillation

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ABSTRACT

Background and Objectives: Left atrial (LA) fibrosis is an important component of the arrhythmogenic substrate and is related to LA dysfunction in patients with atrial fibrillation (AF). However, its relationship with functional changes and the risk of thrombus in patients with paroxysmal AF (PAF) and persistent AF (PeAF) remains unclear.
Methods: We included 139 patients with preprocedural cardiac magnetic resonance imaging (CMR) and transesophageal echocardiography (TEE) for the first AF catheter ablation. Spontaneous echo contrast (SEC) and multiple parameters of LA were measured from TEE and CMR. LA fibrosis was evaluated by late gadolinium enhancement of LA (LA-LGE) of CMR.
Results: The presence of SEC was higher in patients with PeAF than in patients with PAF (26.4% vs. 11.9%, p=0.03). The patients with SEC had more enlarged LA size and impaired function of LA and LAA, regardless of AF type. However, the area of LA-LGE was more extensive in patients with SEC in PeAF (27.5±15.9 vs. 20.1±10.3, p=0.033), not in PAF. In PAF, maximal LA volume index was closely related to the presence of SEC with marginal trend toward significance (odd ratio [OR], 1.07; 95% confidence interval [CI], 0.99–1.16; p=0.072). Whereas, a larger area of LA-LGE and lower emptying flux of LA appendage were independently related with SEC (OR, 1.10; 95% CI, 1.0–1.20; p=0.049 and OR, 0.93; 95% CI, 0.86–0.99; p=0.022, respectively) after adjusting related cardiovascular risk factors of SEC
Conclusions: In this study, we suggest that the risk of thrombus is provoked by LA enlargement with dysfunction in early-stage AF and by stiffened LA with fibrosis rather than LA size when it becomes PeAF.

Keywords: Atrial fibrillation; Left atrial function; Spontaneous echo contrast

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Kim HD, Cho DH, Kim MN, Choi JI, Park SM; Data curation: Kim HD, Hwang SH, Shim J, Choi JI, Kim YH; Formal analysis: Kim HD, Cho DH, Park SM; Investigation: Kim HD, Kim MN; Methodology: Kim HD, Kim MN; Project administration: Park SM; Supervision: Kim MN, Kim YH, Park SM; Validation: Kim HD, Cho DH, Kim MN, Choi JI, Kim YH, Park SM; Visualization: Kim HD, Cho DH, Hwang SH, Park SM; Writing - original draft: Kim HD; Writing - review & editing: Kim HD, Park SM.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in worldwide.[1] The risk of ischemic stroke is 5-fold higher in patients with AF than those in those without AF,[2][3] and stroke occurred 4% per year on a study with prospective registry in 46 countries.[4]

Preventing thromboembolic events is important for the treatment of AF, and the risk of thromboembolic events can be evaluated using the $CHADS_2$ or CHA_2DS_2-VASc scoring systems. In addition to these clinical risk score systems, there are several well-known echocardiographic predictors of risk of thromboembolism in patients with AF, such as left ventricular (LV) systolic dysfunction,[5] left ventricular hypertrophy (LVH),[6] increased left atrial (LA) size,[7] LA dysfunction,[8] LA fibrosis,[9][10] and left atrial appendage (LAA) flow velocities.[11][14] However, differences between these parameters in paroxysmal AF (PAF) and persistent AF (PeAF) have not been well investigated for their predictive value in the risk of thromboembolism.

Thus, the purpose of this study was 1) to evaluate the relationship between LA size, function, and fibrosis and the presence of spontaneous echo contrast (SEC) by AF type and 2) to investigate the independent imaging predictor for SEC by AF type.

METHODS

Study population

This study included 182 consecutive patients with non-valvular AF who underwent their first radiofrequency catheter ablation (RFCA) at the Korea University Anam hospital between May 2015 and February 2016. Of the 182 patients originally eligible for the study, we excluded 41 patients who did not undergo cardiac magnetic resonance imaging (CMR) or transesophageal echocardiography (TEE) and 2 patients who could not acquire adequate image quality to analysis. In total 139 patients (ratio of female and male, 27:112; age, 57±10 years) were included in the analysis. The CHA_2DS_2-VASc score was calculated in each patient, and anticoagulation medications were given to patients with a high risk of stroke according to their CHA_2DS_2-VASc score. The physician chose the type of anticoagulants. Transthoracic echocardiogram (TTE), TEE, and CMR were performed within 24 hours of RFCA. Exclusion criteria were as follows: the presence of significant valvular heart disease, severe LV dysfunction, hypertrophic cardiomyopathy, and congenital heart disease. The study was approved by the Institutional Review Board of the Korea University College of Medicine (approval No. 2018AN0055), and written informed consent was waived since current study is based on retrospective analysis.

Echocardiography

Comprehensive 2-dimensional (2D) and Doppler echocardiography studies were performed, including measurements of the cardiac chamber size, LV mass, LV ejection fraction (LVEF), LA volume (LAV), LA emptying fraction (LAEF), early diastolic mitral inflow velocity (E), and septal annular velocity (e′) according to recommendations from the American Society of Echocardiography.[15] Volume parameters were indexed by body surface area.

Each patient also underwent TEE using a GE Medical Health Vivid 9 (GE Healthcare, Chicago, IL, USA) or Philips Healthcare iE33 (Philips Healthcare, Amsterdam, Netherlands) commercially available equipment. LAA emptying and filling velocities were measured

using pulse wave Doppler within a 1 cm orifice of the LAA. Velocities in each RR interval were averaged from at least 5 cardiac cycles. The presence of thrombus was defined as an intracavitary echogenic mass that was distinct from the LAA endocardium and pectinate muscle. SEC was defined as a swirling, smoke-like echogenic material distinct from background white noise caused by excessive gain. The presence of SEC severity was done by primary observer and independent reviewer. Inter-observer variabilities in SEC presence were compromised with consensus.[16-18]

CMR

CMR was performed using a 3.0-T MR machine (Achieva; Philips Medical Systems, Best, Netherlands) using a 32-element phased-array cardiac coil. CMR data were acquired using a contrast-enhanced timing robust angiography sequence without electrocardiogram (ECG) gating after injecting 0.2 mmol/kg of gadolinium contrast agent (Dotarem®; Guerbet SA, Villepinte, France). The maximum and minimum volumes (mL) of LA and LAA were measured using commercially available software (Terarecon iNtuition; TeraRecon, Foster City, CA, USA). CMR voxels corresponding to the LA and LAA were selected based on manually drawn endocardial boundaries of the LA and LAA, respectively. Voxels were used to measure the volumes (mL) of the LA and LAA. In addition, late gadolinium enhancement (LGE)-CMR was performed approximately 15–20 minutes after gadolinium administration.[19]

According to a previously published method, LA-LGE was measured for evaluating LA fibrotic burden.[20] The 3D model of the LA wall was reconstructed from the transverse or coronal images of LGE-CMR. In the quantitative analysis of the selected LA wall, signal threshold methods were used involving the manual delineation of regions of interest (ROI) after semiautomatic contouring. Based on the mean and standard deviation (SD) values from ROI, over the 6-SD threshold was defined as fibrotic substrate. The ratio of the fibrotic substrate from the whole 3D LA wall was calculated as a percentage. For intergroup variance analysis, LA-LGE was categorized into five groups by percentile.

According to a previously published method, LAA emptying flux (LAA-EF) was measured by velocity encoded (VENC) CMR.[19] To evaluate LAA blood flow, LAA was traced in axial view at the level of LAA ostium. The maximum blood flux from the LAA to the LA chamber was considered as LAA emptying flux during the cardiac cycle on VENC CMR data.

Statistical analyses

Continuous data are presented as means ± SD, and categorical variables as numbers and percentile values. Independent sample t-test were performed to compare continuous variables. Categorical variables were compared using χ^2 test. ANOVA test was used to analyze differences of variance in continuous variables by categorical subgroup, and these were verified using Duncan's post-hoc analysis method. Pearson's correlation coefficient analysis was performed to examine correlations between 2 variables.

Univariate logistic regression analyses were performed to evaluate the odds ratio (OR) of LA functional parameters on the presence of SEC, and multivariate logistic regression analyses with backward eliminations were performed to adjust for known predictive factors of thromboembolism (i.e., age, sex, diabetes, hypertension, LVEF, peak LAA emptying flow velocity, anticoagulation treatment).

All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

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RESULTS

Baseline characteristics

The age was not different between patients with PAF and with PeAF. The prevalence of hypertension and coronary artery disease were not different between groups. However, the cerebrovascular accident was prevalent, and diabetes was frequent, an important trend in patients with PeAF (**Table 1**). Therefore CHA_2DS_2-VASc score of patients with PeAF is slightly higher than that of patients with PAF with a statistical trend (0.89±1.06 vs. 1.27±1.25, p=0.070). The AF duration was shorter in patients with PAF than those with PeAF (27.9±27.2 vs. 39.9±35.1 months, p=0.043). Anticoagulants were prescribed more frequently in patients with PeAF than those with PAF (46.2% vs. 75.4%, p=0.001). All baseline characteristics are summarized in **Table 1**.

Echocardiographic findings

All echocardiographic parameters are summarized in **Table 1**. LV size, LV EF, and E/e′ were not significantly different between patients with PAF and PeAF, whereas LA size was larger in patients with PeAF than in those with PAF (**Table 1**).

Table 1. Baseline characteristics of study population

Characteristics	Paroxysmal (n=67)	Persistent (n=72)	p value
Demographic characteristics			
Age	56.8±10.9	57.5±10.0	0.686
Sex (F/M)	14/53	13/59	0.675
AF duration (months)	27.9±27.2	39.9±35.1	0.043
HTN	29 (43.3)	35 (48.6)	0.532
DM	3 (4.5)	10 (13.9)	0.054
CAD	2 (3.0)	1 (1.4)	0.521
CVA	1 (1.5)	7 (9.7)	0.034
CHA_2DS_2-VASc	0.89±1.06	1.27±1.25	0.070
BB	35 (52.2)	27 (37.5)	0.082
CCB	4 (6.0)	9 (12.5)	0.184
ACEi or ARB	16 (23.9)	12 (16.7)	0.736
Statin	13 (19.4)	19 (26.4)	0.247
Antiplatelet	32 (47.8)	20 (27.8)	0.015
Warfarin	9 (13.4)	24 (33.3)	0.005
NOAC	23 (34.3)	32 (44.4)	0.225
TTE findings			
LAD (mm)	39.3±5.5	43.0±4.7	<0.001
LAVI (mL/m^2)	33.6±12.5	40.4±14.0	0.007
LVMI (g/m^2)	90.4±16.7	90.6±17.1	0.949
LVEF (%)	55.7±3.7	54.3±4.9	0.054
E/e′	9.0±2.7	8.3±3.5	0.238
TEE findings			
Peak LAA emptying velocity (cm/s)	52.4±19.9	44.2±22.9	0.026
Peak LAA filling velocity (cm/s)	54.4±21.1	47.3±23.7	0.065
SEC	8 (11.9)	19 (26.4)	0.030
CMR findings			
LAVImax (mL/m^2)	84.8±29.1	96.9±35.2	0.029
LAEF (%)	47.0±15.1	26.9±11.0	<0.001
LA-LGE (%)	17.0±10.8	22.0±12.3	0.016
LAA-EF (mL/s)	58.4±26.8	33.7±21.5	<0.001

Values are expressed as mean ± standard deviation or number (%).
ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-II receptor blocker; BB = beta-blocker; CAD = coronary arterial disease; CCB = calcium channel blocker; CVA = cerebrovascular disease; DM = diabetes mellitus; HTN = hypertension; LAA = left atrial appendage; LAA-EF = emptying flux of left atrial appendage; LAD = left atrial diameter; LAEF = left atrial emptying fraction; LAVI = left atrial volume index; LAVImax = maximal left atrial volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NOAC = novel oral anticoagulant; SEC = spontaneous echo contrast.

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SEC was frequently found in patients with PeAF than in patients with PAF (26.4% vs. 11.9%, p=0.03). The peak emptying velocity of the LAA (LAAEV) was smaller in patients with PeAF than in those with PAF AF (44.2±22.9 vs. 52.4±19.9, p=0.026).

CMR findings

The maximal and minimal LAV were larger and LA emptying fraction (LAEF) was lower in patients with PeAF than in those with PAF (**Table 1**). The LAA-EF was lower in patients with PeAF than in those with PAF AF (33.7±21.5 vs. 58.4±26.8, p<0.001). LA-LGE is larger in patients with PeAF than in those with PAF (22.0±12.3 vs. 17.0±10.8, p=0.016). All parameters of CMR are summarized in **Table 1**.

Difference of LA structure and function by LA fibrosis by AF type

Maximal LAV (F=2.513, p=0.045) and LAEF (F=3.466, p=0.010) were different among subgroups by LA-LGE in all patients. However, these results changed when patients were separated by type of AF. In patients with PAF, the maximal LAV (F=0.954, p=0.440) and LAEF (F=1.031, p=0.399) did not differ by LA-LGE. In addition, in patients with PeAF, the maximum LAV (F=1.358, p=0.261) and LAEF (F=0.622, p=0.649) did not differ from LA-LGE.

Differences of LA structure and function by the presence of SEC by AF type

In the whole study population, patients with SEC had larger LA size (**Table 2**), lower LAEF, and larger LA-LGE than those without SEC (23.6±11.8 vs. 39.7±16.1, p<0.001 and 23.8±15.7 vs. 17.1±11.2, p=0.013, respectively). And LAA emptying velocities by TEE and CMR were slower in patients with SEC than in patients without SEC (**Table 2**)

SEC was observed more frequently in patients with PeAF (26.4% vs. 11.9%, p=0.032). In PAF, the parameters of LA size were increased, and the function of LA and LAA were impaired in patients with SEC than in patients without SEC. However, LA-LGE was not significantly different between patients with and without SEC (18.9±12.5 vs. 16.8±10.6, p=0.613). The tendency for a larger LA and impaired LA and LAA function in patients with SEC was similarly observed in PeAF. And LA-LGE of patients with SEC was higher than patients without SEC in PeAF (27.5±15.9 vs. 20.1±10.3, p=0.033) (**Figure 1**).

The LA structure and function for predicting SEC

In the whole study population, maximal left atrial volume index (LAVImax) and LAA-EF were independently associated with the presence of SEC after adjusting related factors of SEC in univariate analysis (**Table 3**). When analyzed by dividing according to AF type, increased

Table 2. Differences in left atrial parameters by the presence of SEC

Variables	All patients (n=139)			Paroxysmal AF (n=67)			Persistent AF (n=72)		
	SEC (+) (n=24)	SEC (–) (n=115)	p value	SEC (+) (n=8)	SEC (–) (n=59)	p value	SEC (+) (n=16)	SEC (–) (n=56)	p value
ECHO									
LAD (mm)	44.6±4.3	40.4±5.4	<0.001	43.5±5.2	38.8±5.3	0.011	45.1±3.9	42.3±4.8	0.024
LAVI (ml/m^2)	48.6±14.6	34.6±12.2	<0.001	45.8±17.4	32.2±11.2	0.011	49.7±13.8	37.3±12.7	0.002
LAAEV (cm/s)	26.4±10.5	53.4±20.6	<0.001	26.4±8.3	56.0±18.4	<0.001	26.5±11.5	50.6±22.7	0.001
CMR									
LAVImax (ml/m^2)	65.1±19.1	48.0±17.4	<0.001	63.2±22.6	45.9±15.0	0.005	65.9±18.1	50.4±19.7	0.004
LAEF (%)	23.6±11.8	39.7±16.1	<0.001	28.2±15.2	49.6±13.3	<0.001	21.6±10.0	28.7±10.9	0.015
LA-LGE	23.8±15.7	17.1±11.2	0.013	18.9±12.5	16.8±10.6	0.613	27.5±15.9	20.1±10.3	0.033
LAA-EF (cm/s)	26.7±16.6	49.3±27.2	<0.001	33.3±26.6	61.3±25.6	0.014	24.6±12.3	37.1±23.2	0.029

LA-LGE = left atrial late gadolinium enhancement; LAA-EF = emptying flux of left atrial appendage; LAAEV = left atrial appendageal emptying velocity; LAAflux = Left atrial appendageal emptying flux; LAD = left atrial diameter; LAEF = left atrial emptying fraction; LAVI = left atrial volume index; LAVImax = maximal left atrial volume; SEC = spontaneous echo contrast.

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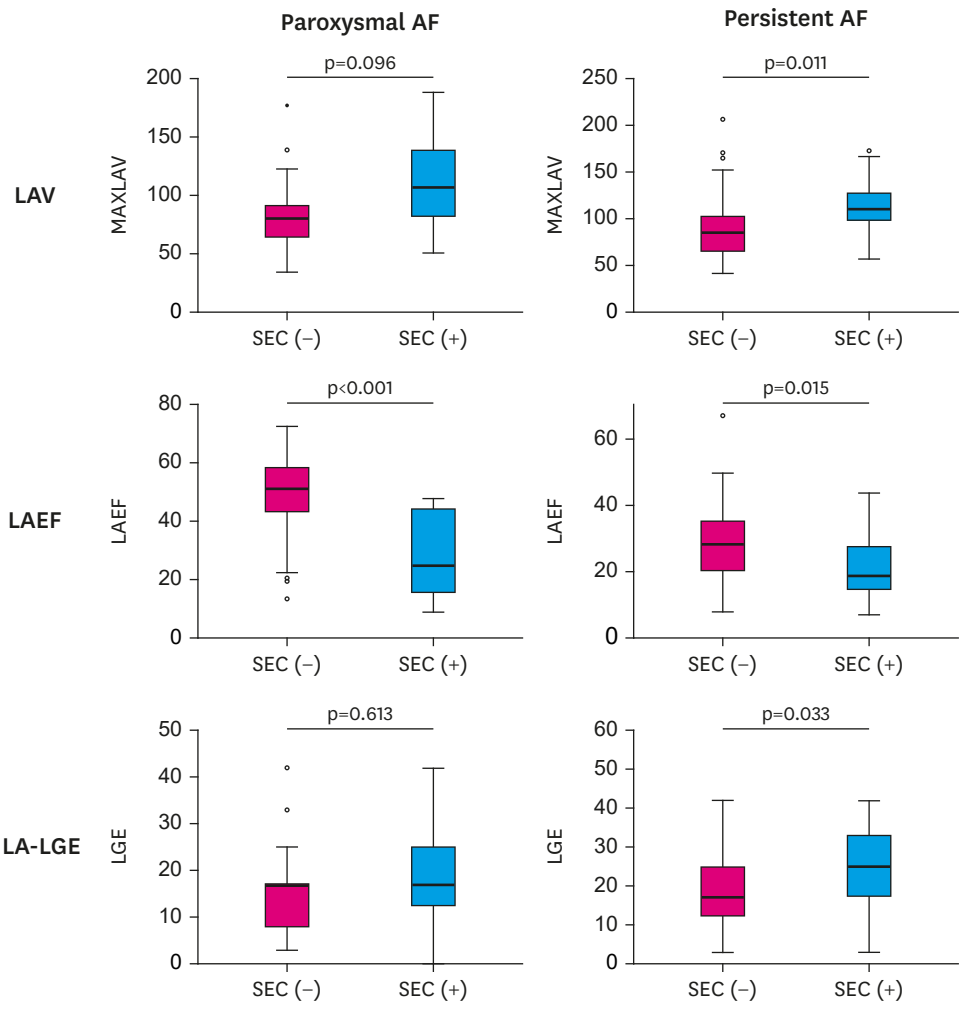

Figure 1. Differences in LA functional parameters between AF patients with or without the presence of SEC.
AF = atrial fibrillation; LA = left atrial; LA-LGE = left atrial late gadolinium enhancement ; LAEF = left atrial emptying fraction; LAV = left atrial volume; SEC = spontaneous echo contrast.

LAVImax had a statistical trend for predicting SEC in patients with PAF (OR, 1.07; 95% confidence interval [CI], 0.99–1.16; p=0.072). On the other hand, a higher amount of LA-LGE and lower LAA-EF have closely related the presence of SEC in patients with PeAF (OR, 1.10; 95% CI, 1.0–1.20; p=0.049 and OR, 0.93; 95% CI, 0.86–0.99; p=0.022, respectively) (**Figure 2**).

DISCUSSION

In this study, we evaluated the relationship between SEC and LA size, function, and fibrosis and compared the predictability of risk of thromboembolism between patients with PAF and those with PeAF. The main findings of this study were, 1) larger LAV and lower LAEF were observed in patients with AF in the presence of SEC; 2) LAVs and the amount of LA fibrosis were significantly larger in patients with PeAF than in those with PAF; however, there was no significant relationship between the LAV and LA fibrosis, particularly in patients with PeAF; 3) the increased amount of LA fibrosis and lower LAA-EF were independent predictors for SEC in patients with PeAF. And larger LAVI was related to the presence of SEC with a statistical trend in patients with PAF.

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Table 3. Imaging parameter for predicting of SEC by multivariate logistic regression analyses

Variables	Whole population (n=139)		Paroxysmal AF (n=67)		Persistent AF (n=72)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
LVEF	0.91 (0.81–1.02)	0.109	0.84 (0.63–1.11)	0.223	0.79 (0.63–1.00)	0.051
LAVImax	1.05 (1.02–1.08)	0.002	1.07 (0.99–1.16)	0.072	1.04 (0.99–1.09)	0.130
LAEF	0.99 (0.95–1.04)	0.637	0.97 (0.88–1.07)	0.552	0.91 (0.81–1.02)	0.088
LA-LGE	1.04 (0.99–1.08)	0.101	1.03 (0.93–1.15)	0.523	1.10 (1.0–1.20)	0.049
LAA-EF	0.96 (0.93–0.99)	0.012	0.95 (0.90–1.01)	0.131	0.93 (0.86–0.99)	0.022

Multivariate logistic regression analysis was analyzed with adjusting related factors of SEC among age, sex, hypertension, diabetes, cerebrovascular accident, vascular disease, and the use of anti-coagulation were by univariate logistic regression.
AF = atrial fibrillation; CI = confidence interval; LA-LGE = left atrial late gadolinium enhancement; LAA-EF = emptying flux of left atrial appendage; LAEF = left atrial emptying fraction; LAVImax = maximal left ventricular volume index; LVEF = left ventricular ejection fraction; OR = odds ratio; SEC = spontaneous echo contrast.

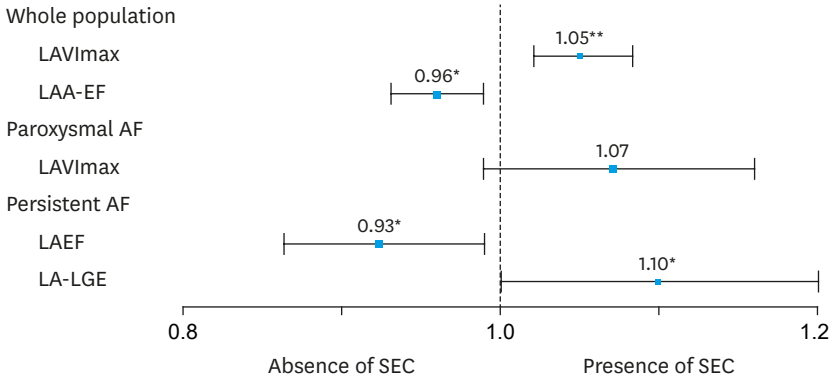

Figure 2. Plots for odds ratios in the presence or absence of SEC; final model with multivariate analysis.
LA-LGE = left atrial late gadolinium enhancement; LAA-EF = emptying flux of left atrial appendage; LAEF = left atrial emptying fraction; LAVImax = maximal left atrial volume index; SEC = spontaneous echo contrast.
*p<0.05, **p<0.01.

In our study population, the prevalence of SEC in LA and LAA was 11.9% in patients with PAF and 26.4% in patients with PeAF. Balouch et al.[21] reported an assessment of trends in TEE use, rate of LAA thrombus in pre-procedure TEE. In that study, they reported that TEE was performed in 646 of 1,224 AF ablation cases (52.8%), and SEC was found in 91 of 576 patients (15.8%) with pre-procedural anticoagulation use in 942 of 999 cases (94.3%). In an article about LAA thrombus found on preprocedural TEE for AF ablation during direct oral anticoagulant by Harada et al.,[22] they reported that SEC was found in 64 of 407 total AF patients on pre-procedural oral anticoagulant therapy (15.7%). They also noted that SEC was found in 57 of 389 patients without LAA thrombus (12.1%). These results are consistent with our study population, which also has a high pre-procedural oral anticoagulation therapy.

Thromboembolisms that arise from LA and LAA are a significant cause of mortality and morbidity in patients with AF.[23] For clinical risk stratification, the $CHADS_2$ or CHA_2DS_2-VASc scoring systems have been commonly used since the 2012 European Society of Cardiology (ESC) guidelines focused update.[24] However, these scoring systems remain limited as because there are no considerations about hemodynamic and structural impairment that are frequently observed in patients with AF, particularly LA enlargement,[25-27] LA dysfunction,[8][28] LA fibrosis,[9][10] decreased LAA emptying flow velocity[12][14] are common features.

Several studies[11-14] have also showed that decreased LAA emptying flow velocity is associated with dense SEC and an elevated risk of stroke. Zabalgoitia et al.[13] performed a cross-sectional analysis of TEE features with traditional thromboembolic risk factors for non-valvular AF, including old age, hypertension, heart failure, and previous thromboembolic events.

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The authors reported that the higher the traditional thromboembolic risk is related to the presence of LAA thrombus, the slower LAA peak flow velocities (≤20 cm/s), dense SEC, and complex aortic plaques. In addition, Handke et al.[14] reported that LAA emptying velocity is dependent on the type of cardiac rhythm, which is faster in sinus rhythm than in PAF, and faster in PAF than chronic AF. This study also revealed a relationship between the LAA emptying velocity and the presence of SEC or thrombus in LA and LAA.[14] In early studies about the risk factors for stroke in atrial fibrillation, most researchers focused on the LA size. Caplan et al.[25] showed that the left atrial size was larger in AF patients with stroke than those without stroke. Moulton et al.[26] also showed that LA enlargement was an independent risk factor for stroke in nonrheumatic AF. Because LA enlargement has also been recognized as a risk factor for recurrent AF in a study based on AFFIRM trial results,[27] LA enlargement is now believed to be an essential risk factor of thromboembolism in patients with AF.

Conversely, the role of LA function in AF has not received attention until relatively recently. Inaba et al.[28] suggested using strain rate imaging of the LA as a functional quantification and showed that the peak systolic strain rate of LA was decreased in patients with PeAF. In a study of 169 AF patients, Inoue et al.[8] showed that decreased LA reservoir function assessed using quantitative tissue-tracking CMR was significantly associated with a prior history of stroke or transient ischemic attack. Kim et al.[29] also reported that impaired LA function has a more excellent additive predictive value to CHA_2DS_2-VASc score for predicting the presence of thrombus or dense SEC. After speckle-tracking echocardiography was developed, Leong et al.[30] reported that measuring the LA reservoir strain had value in identifying cryptogenic stroke. This study also suggested that this finding had clinical implications for patients with asymptomatic AF.

CMR with ECG gated cine imaging can provide information on the LA function, and LA-LGE can also quantify LA fibrosis. Inoue et al. showed that LA reservoir function, as using quantitative tissue tracking CMR, is associated with a history of stroke or TIA in patients with AF. Moreover, in a CMR study, Habibi et al.[9] showed that LA-LGE was correlated with LA emptying fraction and LA strain, and that patients with PAF had better LA function than those with PeAF.

Data from the Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF) study by Marrouche et al.[31] support the concept that LA fibrosis could be an arrhythmogenic substrate of AF. The authors showed that the LA fibrosis percent, adjusted for other risk factors, was closely related to the AF recurrence rate. They also showed that the increased burden of fibrosis was related to an increased cumulative incidence of AF recurrence.[31] This is further supported by conduction slowing in voltage mapping, which may be associated with thick interstitial collagen strands in patients with AF.[10]

Our study compared the correlation between LA-LGE and SEC in patients with paroxysmal and PeAF, and our results showed that LA fibrosis was correlated with SEC only in patients with PeAF. Based on these findings, we suggest that early medical or non-medical intervention of AF would inhibit the progress of atrial fibrosis, which would help prevent stroke or TIA.

LA fibrosis regards to be closely related to increasing LAV and function, in general. In this study, the same correlation was also observed in total patient. However, when we divide

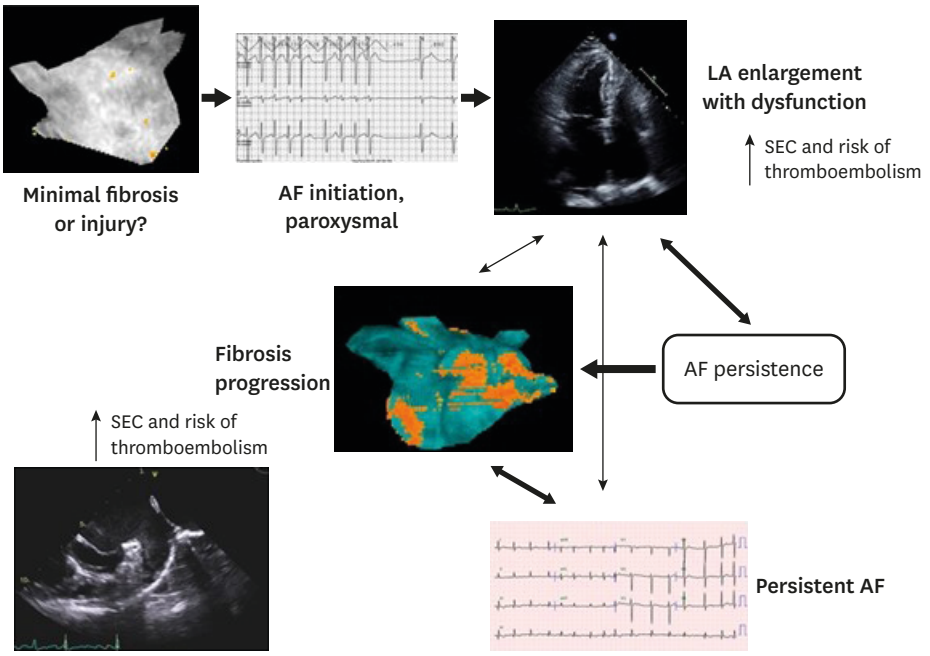

Figure 3. Postulated relationship between LA dysfunction and fibrosis and the risk of thromboembolism in patients with AF. Persistent AF leads to AF and more LA fibrosis. SEC and the risk of thromboembolism is increased by LA dysfunction and LA fibrosis.
AF = atrial fibrillation; LA = left atrial; SEC = spontaneous echo contrast.

patient group by AF types, LA fibrosis was independent from LAEF and volume. With these findings, we regarded that the correlation between SEC and LA fibrosis in patients with PeAF also be independent from LAV and function. In patients with PAF, LA fibrosis was small and SEC was related to LAEF, whereas in patients with PeAF, there was no relationship between LAV and LA fibrosis but SEC was related to LA fibrosis. Therefore, we can infer that LA dysfunction with enlargement but minimal fibrosis presents a risk of thrombus or SEC during the paroxysmal or early stage of AF. However, when AF becomes PeAF, LA becomes more fibrotic and SEC is provoked by a stiffened LA with reduced LAEF, rather than LA size. Thus, AF begets AF PeAF and more LA fibrosis. Therefore, it is important to interrupt this vicious cycle (**Figure 3**).

Recently, the concept of "LA reverse remodeling" has been put forth, which states that early medical or non-medical intervention for AF can stop or reverse the LA remodeling processes such as LA enlargement or LA fibrosis.[32] Some animal studies with heart failure model had shown that spironolactone,[33] angiotensin converting enzyme inhibitors,[34] and angiotensin receptor blockers[35] have effect on reducing LA fibrosis. Thus, follow up studies targeting the change in the burden of fibrosis after medical treatment are currently being considered.

There were several limitations to our study. First, because most of our study patients were referred to the hospital for RFCA and were under anticoagulation therapy, we could not found LA or LAA thrombus. Therefore, we considered SEC as a surrogate marker of thromboembolism. Second, we were able to review 3-year follow-up data for only 60% of total patients and stroke was only observed in one patient with PeAF. This may have occurred because many patients returned to the local clinic after treatment, and most of study patients were maintained anticoagulants even after ablation. Third, our multivariable analysis did not show any significant associations except LAA peak emptying velocity,

which is already known in previous study.[14] Therefore, we attempted to identify at least a trend of association between LA parameters and SEC using backward elimination. For this reason, the significance of analysis is a weakness in our study. Finally, because we included patients with AF who were planned for RFCA, they had preserved LVEF, and LAV was not severely increased. Therefore, this result could be different if other patients were included. In contrast, we were able to eliminate confounding factor of LV dysfunction affecting LA and, thus, were able to infer the role of AF in affecting LA fibrosis, independent of the LAV.

In patients with AF, predicting the risk of thromboembolism is crucial to prevent embolic stroke. SEC was most related to the LAV and LAEF in PAF and to LA fibrosis in PeAF. These findings suggest that the risk of thrombus is provoked by LA enlargement with dysfunction during the paroxysmal or early stage of AF, and when AF becomes PeAF, it causes more LA fibrosis. Thus, the risk is provoked by stiffened LA rather than by LA size.

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