Featured Article

Prognostic implication of left atrial strain in patients experiencing early recurrence of atrial fibrillation after totally thoracoscopic ablation

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Background: Although early atrial fibrillation (AF) events during the blanking period after AF ablation are risk factors for late recurrence, data on predictors of late recurrence in patients who experience early AF events are limited. In this study, we investigated the implications of left atrial (LA) strain with respect to long-term outcomes in patients experiencing early AF during the blanking period after totally thoracoscopic ablation (TTA).

Methods: A total of 128 patients who underwent TTA between 2012 and 2015 were enrolled from a tertiary center. Peak longitudinal LA strain was measured preoperatively. Early recurrence (ER) was defined as any AF within the 3-month blanking period after TTA. The primary outcome was late recurrence of AF for 5 years, detected on 12-lead electrocardiogram or 24-hour Holter monitoring, excluding the blanking period.

Results: Out of 128 patients, 42 (32.8%) experienced ER during the blanking period. Patients who experienced ER had a significantly higher risk of 5-year AF recurrence compared with those who did not [72.7% *vs.* 29.6%, hazard ratio (HR) =3.69, 95% confidence interval (CI): 2.14–6.36, P<0.001]. Within the group of 42 patients experiencing ER, LA strain with a best cutoff value of 18.6% was the only independent predictor of 5-year AF recurrence (adjusted HR =4.20, 95% CI: 1.08–16.29, P=0.038). Patients with ER and LA strain ≥18.6% had a risk of 5-year AF recurrence, similar to those without ER (35.2% *vs.* 29.6%, HR =1.21, 95% CI: 0.36–4.04, P=0.755). Patients with ER and LA strain <18.6% had a significantly higher risk of 5-year AF recurrence compared to those without ER (83.0% *vs.* 29.6%, HR =4.83, 95% CI: 2.75–8.48, P<0.01).

Conclusions: Early AF during the blanking period is common in patients undergoing TTA. In patients with ER, LA strain was an independent predictor of long-term AF recurrence.

Keywords: Atrial fibrillation (AF); thoracoscopic ablation; recurrence; left atrial strain (LA strain)

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia, resulting in increased mortality, morbidity, and poorer quality of life (1,2). For patients who have symptomatic AF refractory to medical therapy, catheter or surgical ablation has emerged as an effective option for rhythm control (3-5). Early recurrence (ER) after ablation therapy has been recognized. Reportedly, as many as 61% of patients experience ER of arrhythmia (6-10). As ER is believed to be benign and related to transient local inflammatory and pro-arrhythmic states, reintervention is not recommended during the "blanking period" of the initial 3 months after ablation (4). However, increasing evidence suggests that patients with ER have a higher risk of late recurrence (6,8,10-12). While various predictors of ER after ablation have been proposed, such as left atrial (LA) enlargement, non-paroxysmal AF, or comorbidities (13,14), limited data exists on predictors of late recurrence in patients who experience ERs. Therefore, identifying predictors of late recurrence in patients who experience ERs is crucial for improving patient outcomes. Totally thoracoscopic ablation (TTA) has recently been highlighted as an effective option with minimal invasiveness. Although favorable outcomes of TTA have been reported (15-17), recurrence after a successful initial procedure remains problematic. However, in most studies, the blanking period was excluded from the definition of AF recurrence (15,17-19). As ER after Maze procedure is a predictor of late failure (20-22), ER after TTA may be clinically significant. To date, the frequency and prognosis of ER after TTA for AF are unknown. In this study, we investigate the clinical significance of early AF events during the blanking period and the role of preoperative LA strain in predicting late recurrence.

Methods

Study population

Between February 2012 and March 2015, patients undergoing TTA were enrolled in a prospective registry in the Samsung Medical Center, Republic of Korea. Patients with AF refractory to at least 1 antiarrhythmic drug or electrical cardioversion were candidates for TTA. The indications for TTA also included refractory symptoms, history of stroke, or intolerance of anticoagulant therapy. TTA was contraindicated in patients with LA thrombi or intolerance of one-lung ventilation. Among the 150 consecutive patients who underwent TTA during the study period, three patients who did not undergo an adequate surgical procedure due to a sizable LA or severe pericardial adhesion, one patient who underwent LA appendage (LAA) resection alone for stroke prevention, 17 patients who did not undergo LAA resection during the surgery, and one patient who did not have adequate echocardiographic images for strain measurement were excluded; the final analysis included 128 patients (*Figure 1*). The Samsung Medical Center Institutional Review Board approved the present study (No. 2020-05-146-003).

Thoracoscopic procedures

TTA is a video-assisted thoracoscopic surgical technique without thoracotomy and cardiopulmonary bypass. A bilateral approach is required and the detailed techniques of TTA have been described in our previous report (23). Ablation lines for pulmonary vein isolation were created using an AtriCure Isolator Transpolar Clamp (AtriCure, Inc., Cincinnati, OH, USA) and the LA roof and floor lesions connecting both pulmonary veins were drawn with a linear pen device (AtriCure, Inc.). After creating pulmonary vein isolation and box lesions, exit and entrance block tests using an AtriCure Cooltip pen (AtriCure, Inc.) were performed. Next, the ganglionated plexuses were examined and ablated. The ligament of Marshall, which might be a source of adrenergic atrial tachycardia, was always divided and ablated. The LAA was removed by stapling with an Echelon Flex 60 articulating endoscopic linear stapler (Ethicon Endo-Surgery Inc., Cincinnati, OH, USA).

Postoperative care and endpoint

Patients were monitored in the intensive care unit for the first 24 hours. Heparin was administered after 2 hours postoperatively, and patients were switched to either warfarin or a direct-acting oral anticoagulant as soon as possible. Oral amiodarone was prescribed if the heart rate was >80 beats/min with AF rhythm at rest. Patients were followed up at 3, 6, and 12 months, and annually thereafter with 24-hour Holter monitoring. Antiarrhythmic drugs were discontinued after 3 months or up to 6 months based on the 24-hour Holter monitoring results.

Anticoagulants were also discontinued after 3 months based on the risk of stroke for each patient. ER was defined as any AF or atrial flutter (AFL) detected on electrocardiogram or lasting more than 30 seconds in 24-hour Holter monitoring during the blanking period (initial

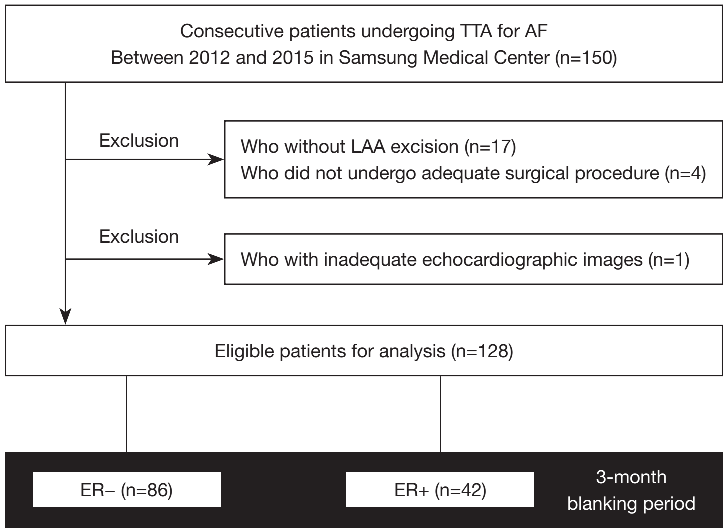

Figure 1 Study population. TTA, totally thoracoscopic ablation; AF, atrial fibrillation; LAA, left atrial appendage; ER, early recurrence.

3 months after TTA). If hybrid (planned) radiofrequency ablation was performed, the blanking period began after the last procedure. ERs were managed using electrical cardioversion or antiarrhythmic drugs. AF or AFL events after the blanking period were defined as late recurrence. Patients were followed up for 5 years after TTA and the median follow-up duration of study subjects was 5.0 years.

Echocardiography and speckle tracking imaging

Preoperative comprehensive transthoracic echocardiography was performed with commercially available equipment (Vivid 7, GE Medical Systems, Milwaukee, WI, USA, Acuson Sequoia 512, Siemens Medical Solution, Mountain View, CA, USA, or Sonos 5500, Philips Medical System, Andover, MA, USA) according to practice guidelines (24). Left ventricular (LV) end-diastolic and end-systolic diameter as well as LA diameter were calculated from parasternal long-axis view. LV ejection fraction was calculated from two-dimensional recordings using the modified biplane Simpson's method. LA volume was assessed using the modified biplane area-length method and indexed to body surface area (LA volume index, LAVI). Early diastolic mitral inflow velocity (E) was measured using the pulsed wave Doppler method by placing the sample volume at the level of the mitral valve leaflet tips. The tissue Doppler-derived early diastolic mitral annular velocity (e') was measured from the septal corner of the mitral annulus in the apical four-chamber view. For patients with AF rhythm, the average of five consecutive Doppler signals was used.

Peak longitudinal LA strain (reservoir strain) was measured using vendor-independent dedicated software (2D cardiac Performance Analysis 1.4, TomTec Imaging Systems, GmbH, Unterschleißheim, Germany) according to the current guideline (Figure S1) (25). Peak positive strain rate was calculated during LV systole. The LA endocardial border was automatically traced by the software and then manually adjusted in both apical four- and two-chamber views. Pulmonary veins and LAA orifices were carefully excluded. The regions of interest encompassed the endocardial border of the mitral annulus, and the thickness of regions of interest was adjusted to the thinnest part to adapt to the atria. Two independent echocardiologists blinded to clinical status analyzed the data. All strain values were calculated from cardiac cycle with heart rate <110 beats per minute to avoid inadequate LA emptying or filling. LA stiffness index was defined as E/e' divided by peak longitudinal LA strain (26).

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median [interquartile range (IQR)]. Categorical variables were compared using the chi-square test. Continuous variables were compared using the Student's *t*-test or Mann-Whitney *U* test as appropriate.

The incidence of recurrent AF or AFL at 5 years after TTA were estimated using the Kaplan-Meier method. Survival curves were compared with the log-rank test. Independent predictors for 5-year AF or AFL recurrence were analyzed using the univariable and multivariable Cox regression models.

Variables with P value <0.2 between patients with and without 5-year AF or AFL recurrence (LAVI, LA strain, and LAA fibrosis area) or clinically relevant variables (age, sex, paroxysmal AF, and radiofrequency catheter ablation) were included in the multivariable Cox regression model. The best cutoff value of LA strain to maximize the difference in 5-year recurrence rate was estimated by plotting the standardized log-rank statistic. All tests were two-sided and a P value <0.05 was considered statistically significant. Statistical analysis was performed using R 3.6.2 (R Foundation for Statistical Computing, https://www.r-project.org/).

Results

Baseline characteristics

A total of 128 patients were eligible for analysis (*Figure 1*). The mean age was 54.3±8.8 years, 95.3% were male, and 18.8% had paroxysmal AF (*Table 1*). The median LA diameter, LAVI, and LA strain were 45.0 mm (IQR, 40.0–50.0 mm), 45.2 mL/m^2 (IQR, 36.4–54.8 mL/m^2), and 15.3% (IQR, 12.1–19.2%), respectively. Among the 128 patients, 42 (32.8%) experienced ER during the blanking period. The median time to ER was 16.5 days (IQR, 8.0–34.5 days). Patients with ER had a significantly larger LAVI compared with those without ER (51.2 *vs.* 42.7 mL/m^2). Other clinical or echocardiographic variables were not significantly different between patients with and without ER. Operative characteristics based on ER are presented in Table S1.

Late recurrence in patients with and without ER

During the 5-year follow-up after TTA, patients with ER had a significantly higher risk of recurrent AF or AFL compared with those without ER [72.7% *vs.* 29.6%; hazard ratio (HR) =3.69, 95% confidence interval (CI): 2.14–6.36, P<0.001; *Figure 2*].

Predictors of late recurrence in patients with ER

Out of the 42 patients with ER, 30 (71.4%) had late recurrence of AF or AFL after the blanking period, while 12 (28.6%) did not have late recurrence. *Table 2* shows baseline differences between patients with and without late recurrence. Among clinical, echocardiographic, and histologic variables, only LA strain showed a significant difference between patients with late recurrence and those without (median value, 13.2% *vs.* 17.8%, P=0.032). The best cutoff value of LA strain for predicting late recurrence was 18.6% (Figure S2 and *Figure 3A*). In multivariable Cox analysis, preoperative LA strain <18.6% was an independent predictor of late recurrence after the blanking period (adjusted HR =4.20, 95% CI: 1.08–16.29, P=0.038; *Table 3*).

Late recurrence based on LA strain

Among the patients with ER, those with LA strain <18.6% had a significantly higher risk of late recurrence compared to those without ER (83.0% *vs.* 29.6%, HR =4.83, 95% CI: 2.75–8.48, P<0.001). However, for patients with ER and LA strain ≥18.6%, the risk of late recurrence was similar to that of patients without ER (35.2% *vs.* 29.6%, HR =1.21, 95% CI: 0.36–4.04, P=0.755; *Figure 3B*).

Discussion

This is the first study to describe the prognostic implication of LA strain in patients with ER after TTA. The main findings of this study were as follows: the incidence of ER during the 3-month blanking period after TTA was 32.8%, patients with ER had a larger LAVI than those without ER, and preoperative LA strain was an independent predictor of late recurrence in patients with ER. Patients with ER but LA strain ≥18.6% had a late recurrence risk similar to those without ER. When energy is delivered to the myocardium to disrupt LA conduction, pathophysiological processes occur, such as coagulative necrosis, perfusion change due to artery trauma, thromboembolism, coronary spasm, oxidative stress, edema, or inflammation (27). These processes and electrical reconnection in LA contribute to arrhythmogenesis associated with ER after ablation. Early atrial arrhythmias during the blanking period, generally defined as the initial 3 months after ablation, are usually considered benign. While aggressive treatment for ER is not recommended because up to half of the patients with ER remain AF-free during long-term follow-up (4), identifying risk factors for ER is clinically important because observational studies have shown a relationship

Table 1 Baseline characteristics based on ER during the 3-month blanking period

Variables	Overall (n=128)	ER (+) (n=42)	ER (–) (n=86)	P value
Clinical				
Age	54.3±8.8	54.5±8.5	54.2±8.9	0.861
Body mass index, kg/m^2	25.2±2.8	25.0±3.0	25.1±2.2	0.893
Male	122 (95.3)	39 (92.9)	83 (96.5)	0.636
Hypertension	49 (38.3)	18 (42.9)	31 (36.0)	0.582
Diabetes	12 (9.4)	2 (4.8)	10 (11.6)	0.353
Previous stroke	19 (14.8)	5 (11.9)	14 (16.3)	0.697
Paroxysmal AF	24 (18.8)	5 (11.9)	19 (22.1)	0.252
$CHADS_2$ score	1.0 [0.0–2.0]	1.0 [0.0–1.0]	1.0 [0.0–1.0]	0.860
CHA_2DS_2 VASc score	1.0 [0.0–2.0]	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.633
NT-proBNP, pg/mL	254.8 [150.9–460.7]	267.1 [175.7–435.0]	253.0 [144.2–462.8]	0.895
Antiarrhythmic drugs before surgery	96 (75.0)	30 (71.4)	66 (76.7)	0.931
Previous RFCA	20 (15.6)	3 (7.1)	17 (19.8)	0.112
Hybrid RFCA	91 (71.1)	33 (78.6)	58 (67.4)	0.273
Echocardiographic				
LVEDD, mm	52.0 [49.0–54.5]	52.0 [50.0–54.0]	51.0 [49.0–55.0]	0.748
LVESD, mm	32.5 [30.0–35.0]	32.5 [30.0–35.0]	32.5 [30.0–36.0]	0.917
LVEF, %	60.0 [56.0–64.0]	59.5 [56.0–64.0]	60.0 [56.0–65.0]	0.837
E/e’	8.2 [6.3–10.1]	8.3 [6.3–10.2]	8.1 [6.3–10.0]	0.847
LAD, mm	45.0 [40.0–50.0]	46.0 [42.0–53.0]	44.0 [40.0–49.0]	0.119
LAVI, mL/m^2	45.2 [36.4–54.8]	51.2 [41.7–59.6]	42.7 [35.3–51.3]	0.011
LA strain, %	15.3 [12.1–19.2]	14.3 [11.8–17.0]	16.2 [12.4–20.2]	0.077
Stiffness index, %	0.5 [0.4–0.8]	0.6 [0.4–0.8]	0.5 [0.4–0.8]	0.222
Histologic				
LAA fibrosis area, %	38.6 [33.1–44.7]	38.2 [34.3–43.9]	38.6 [32.8–46.7]	0.945

Values are presented as mean ± SD, median [interquartile range] or n (%). ER, early recurrence; AF, atrial fibrillation; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; LA, left atrial; RFCA, radiofrequency catheter ablation; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LAVI, left atrial volume index; LAA, left atrial appendage.

between ER and an increased risk of late recurrence (6,13,28,29). Previous studies have suggested that older age, male sex, larger LA, and non-paroxysmal AF are risk factors for developing ER after catheter ablation (7,29,30).

Thoracoscopic ablation was proposed as an effective rhythm control strategy due to the wide range of contiguous ablation and LAA exclusion that can be achieved through minimally invasive surgery. Observational studies and randomized trials have shown favorable outcomes of TTA (31-33). However, the frequency and clinical significance of ER after TTA has not been known, as previous studies excluded the blanking period when defining recurrent events (15,33,34). In the present study, we found that 32.8% of patients experienced ER within 3 months after TTA, and ER was associated with a 3.7-fold increase in the risk of late recurrence. These findings are consistent with studies on

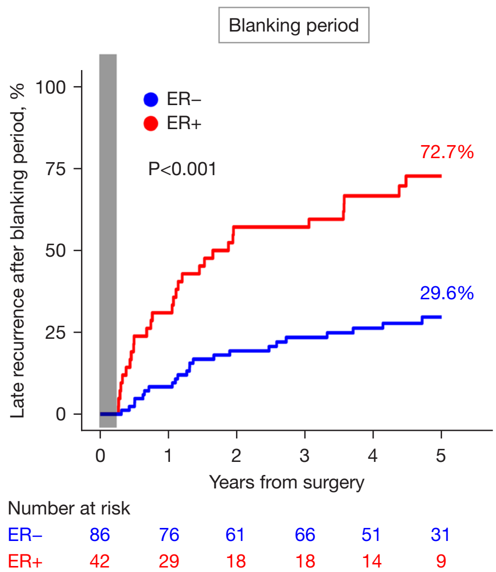

Figure 2 Late recurrence in patients with and without ER. Early recurrence was defined as any AF or AFL during the 3-month blanking period after TTA. AF, atrial fibrillation; AFL, atrial flutter; ER, early recurrence; TTA, totally thoracoscopic ablation.

the Maze procedure. The reported incidence of ER within 3 months after Maze procedure has ranged from 28–49%, and it has been associated with more than 3-fold increase in late recurrence (20-22). Enlarged LA has consistently been identified as a risk factor for the development of ER (13,20,35). However, in previous studies on this issue, only LA diameter and not LAVI was reported as an echocardiographic parameter of LA remodeling (7,9-12,21). In the present study, we found that LAVI, and not LA diameter, was significantly higher in patients with ER. Although the LA anteroposterior dimension is the most widely used and reproducible measurement method, the assessment of LA size using only LA diameter assumes that all its dimensions change similarly when the LA enlarges, which is often not the case during LA remodeling (36). Therefore, the LAVI may provide more prognostic information than the LA diameter for predicting ER in patients undergoing thoracoscopic ablation.

Although the relationship between ER and an increased risk of late recurrence has been suggested, predictors of late recurrence in patients who experience ER after surgical ablation remain unknown. This topic has been investigated in several catheter ablation studies. For instance, a study by Jiang *et al.* reported that smaller LA size and lower P wave dispersion were predictors of delayed cure of ER (35). However, the delayed cure in that study was defined as maintenance of sinus rhythm for more than 2 months after ER, which did not represent long-term late recurrence. Tobacco use was also identified as a risk factor for late recurrence among patients with ER in another study (30), but its clinical usefulness is questionable. Additionally, the timing of ER, generally occurring after the first month of the blanking period, has been suggested to be a risk factor for late recurrence (8,29,37).

Advances in two-dimensional speckle-tracking software have enabled assessment of cardiac chamber deformation and myocardial function beyond the structural remodeling of the LA. LA strain has been studied extensively for its prognostic value in predicting successful electrical cardioversion (38) or catheter ablation (39). However, there has been relatively less research on the role of LA strain in surgical AF ablation. In the present study, preoperative peak LA strain emerged as an independent predictor of late recurrence in patients with ER. Among patients with LA strain ≥18.6%, ER did not pose a significant risk for late recurrence after the blanking period. In contrast, the risk of late recurrence after the blanking period was very high (83.0%) when patients with LA strain <18.6% experienced ER. In agreement with previous studies (30,35), LA enlargement was not found to be a significant predictor of late recurrence in patients with ER in the present study. These findings suggest that functional parameters, such as LA strain, may provide additional prognostic information for determining further treatment of ER following ablation.

The present study had several limitations. Firstly, this was a single-center retrospective study, which may limit the generalizability of the findings to other centers with different patient populations and physician experience with thoracoscopic ablation. Secondly, although annual Holter monitoring is recommended at our institution for all patients undergoing TTA, 24-hour Holter monitoring was not performed systematically in this study due to its observational nature. However, 84.4% of the patients (108 of 128) had undergone 24-hour Holter monitoring, with a median of four monitoring per patient, and the remaining patients had multiple electrocardiograms at each visit. Nonetheless, the possibility of asymptomatic paroxysmal AF cannot be ruled out completely. Thirdly, the best cutoff value of LA strain may vary depending on the quality of echocardiography images, the level of experience in delineating regions of interests, or speckle-tracking software used (25).

Table 2 Baseline characteristics based on late recurrence among patients who experienced ER (n=42)

Variables	Recurrence group (n=30)	Non-recurrence group (n=12)	P value
Clinical			
Age	55.0±8.4	53.2±9.0	0.546
Body mass index, kg/m^2	25.5±2.6	26.1±3.4	0.505
Male	27 (90.0)	12 (100.0)	0.636
Hypertension	13 (43.3)	5 (41.7)	>0.999
Diabetes	1 (3.3)	1 (8.3)	>0.999
Previous stroke	4 (13.3)	1 (8.3)	>0.999
Paroxysmal AF	3 (10.0)	2 (16.7)	0.940
$CHADS_2$ score	1.0 [0.0–1.0]	0.5 [0.0–1.5]	0.835
CHA_2DS_2 VASc score	1.0 [0.0–1.0]	1.0 [0.0–1.5]	0.859
NT-proBNP, pg/mL	280.6 [190.2–482.1]	198.5 [151.8–344.2]	0.208
Antiarrhythmic drugs before surgery	22 (73.3)	8 (66.7)	0.957
Previous RFCA	2 (6.7)	1 (8.3)	>0.999
Hybrid RFCA	25 (83.3)	8 (66.7)	0.440
Echocardiographic			
LVEDD, mm	53.0 [50.0–54.0]	50.0 [47.5–55.0]	0.219
LVESD, mm	32.5 [31.0–35.0]	32.5 [29.5–35.0]	0.634
LVEF, %	60.5 [56.0–64.0]	57.5 [56.0–64.0]	0.511
E/e'	8.8 [6.9–10.4]	7.7 [6.0–8.8]	0.252
LAD, mm	46.0 [42.0–54.0]	46.5 [40.0–52.0]	0.889
LAVI, mL/m^2	55.0 [41.0–62.0]	47.8 [42.1–52.5]	0.129
LA strain, %	13.2 [11.3–15.5]	17.8 [13.9–20.5]	0.032
<18.6%	27 (90.0)	6 (50.0)	0.015
Stiffness index, %	0.6 [0.5–0.8]	0.4 [0.3–0.5]	0.222
Hybrid RFCA	58 (67.4)	33 (78.6)	0.273
Histologic			
LAA fibrosis area, %	38.5 [35.4–46.8]	36.6 [31.2–41.8]	0.179

Values are presented as mean ± SD, median [interquartile range] or n (%). ER, early recurrence; AF, atrial fibrillation; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; RFCA, radiofrequency catheter ablation; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LAVI, left atrial volume index; LA, left atrial; LAA, left atrial appendage.

Nonetheless, this is the first study in which the frequency of ER after thoracoscopic ablation has been investigated. The results suggest that LA strain is a potential predictor of late recurrence in patients with ER following ablation therapy. Future large-scale studies are needed to confirm the current findings.

Conclusions

ER during the blanking period was a significant risk factor

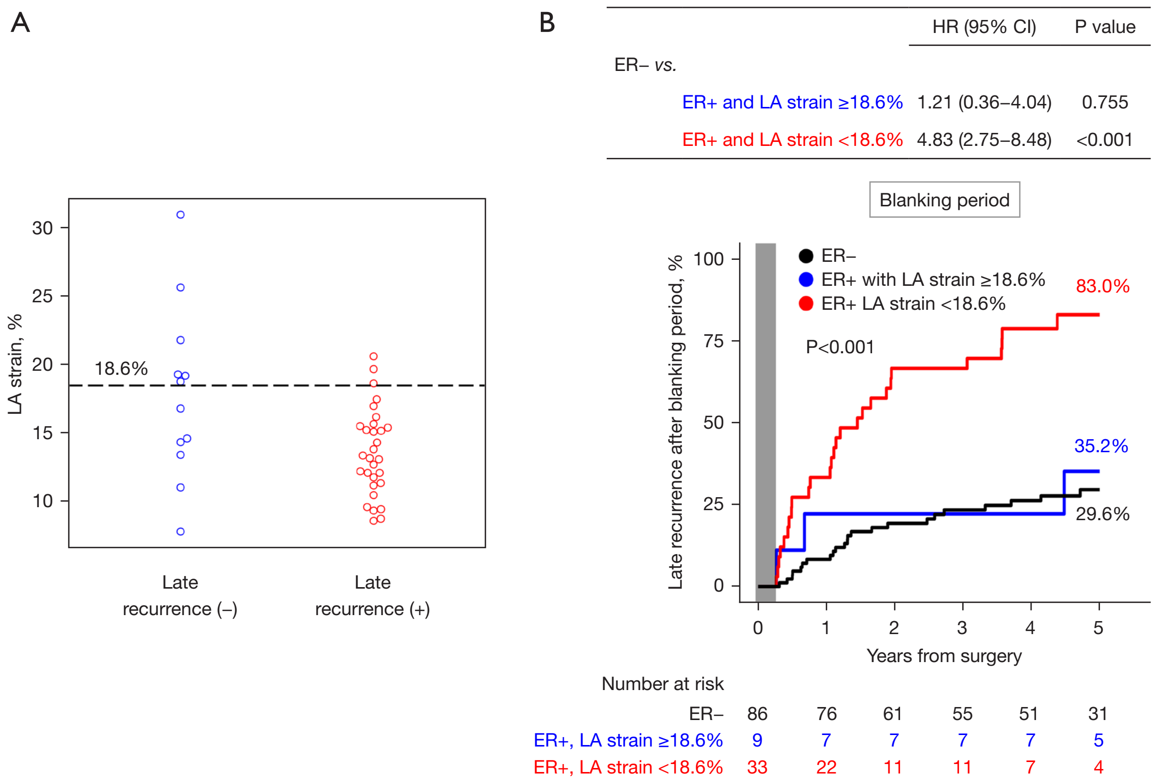

Figure 3 Late recurrence based on LA strain and ER. (A) LA strain in patients with and without late recurrence among those who experienced ER; (B) incidence of late recurrence compared among three patient groups: those without ER, those with ER and LA strain ≥18.6%, and those with ER and LA strain <18.6%. HR, hazard ratio; CI, confidence interval; ER, early recurrence; LA, left atrial.

Table 3 Independent predictors of 5-year AF recurrence in patients who experienced ER

Variables	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (0.96–1.05)	0.800		
Male	0.68 (0.20–2.27)	0.529		
Paroxysmal AF	0.58 (0.18–1.93)	0.376		
Pre or post RFCA	1.10 (0.42–2.88)	0.847		
LAVI, per 1 mL/m^2	1.02 (0.99–1.05)	0.309		
LA strain <18.6%	4.10 (1.22–13.73)	0.022	4.20 (1.08–16.29)	0.038
LA appendage fibrosis, per 1%	1.04 (0.99–1.09)	0.135		

All the listed variables were included in the multivariable Cox regression model. When a backward elimination method was used, only LA strain <18.6% remained in the model. AF, atrial fibrillation; ER, early recurrence; HR, hazard ratio; CI, confidence interval; LA, left atrial; LAVI, left atrial volume index.

for late recurrence in patients undergoing TTA. LA strain was found to be an independent predictor of late recurrence in patients with ER.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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