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Ability of Left Atrial Distensibility after Radiofrequency Catheter Ablation to Predict Recurrence of Atrial Fibrillation

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Running head: Left atrial distensibility

Abstract: This study sought to assess the left atrial (LA) functional recovery after radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) and to evaluate the determining factor of procedural success of RFCA using a novel preload stress echocardiography. A total of 111 patients with AF were prospectively recruited. The echocardiographic parameters were obtained during the leg-positive pressure (LPP) maneuver both at baseline and mid-term after RFCA. As an index of LA distensibility, the LA expansion index was calculated as (LAV_{max} - LAV_{min}) × 100 / LAV_{min}. During a median follow-up period of 14.2 months, AF recurrence was observed in 23 (20.7%) patients. In LA functional parameters at baseline, only the Δ LA expansion index was significantly larger in the success group (16 ± 11% vs. 4 ± 9%, P<0.05). At mid-term follow-up, the Δ LA expansion index significantly increased to 32 ± 19% (P<0.05), together with structural LA reverse remodeling only in the success group. Moreover, the Δ stroke volume index during the LPP stress test significantly increased only in the success group (from 2.3 ± 1.3 mL/m^2 to 3.1 ± 4.8 mL/m^2, P<0.05). In a multivariate analysis, left ventricular ejection fraction (hazard ratio 0.911, P<0.05) and baseline Δ LA expansion index (hazard ratio 0.827; P<0.001) were independent predictors of AF recurrence. In conclusion, the baseline Δ LA expansion index during LPP stress is a reliable marker for predicting procedural success after RFCA. Moreover, maintenance of sinus rhythm resulted in an improvement of the preload reserve after RFCA.

Keywords: leg-positive pressure stress, left atrial distensibility, left atrial fibrosis.

The principal role of the left atrium (LA) is to modulate left ventricular (LV) diastolic filling and cardiac performance through reservoir, conduit, and booster pump functions,[1] without an elevation in LA pressure. In patients with atrial fibrillation (AF), these essential functions are significantly impaired, leading to LA remodeling. Structural LA remodeling progressively leads to myocardial dysfunction and subsequent electrical alterations in the cardiomyocytes,[2] creating an AF-prone fibrotic substrate,[3] which promotes trigger driven paroxysmal to substrate dependent persistent AF. The purpose of this study was to assess the relationship between maintenance of sinus rhythm and functional LA reverse remodeling mid-term after radiofrequency catheter ablation (RFCA). Moreover, we also investigated the determinant factor for predicting procedural success of RFCA by preload stress echocardiography using a novel leg-positive pressure (LPP) maneuver.

Methods

This prospective study included 111 consecutive patients with AF who underwent RFCA at the Kobe University Hospital and Tokushima University Hospital from October 2018 to March 2020. The exclusion criteria for this study were (1) a suboptimal quality of echocardiographic images, (2) history of venous thrombosis or pulmonary embolism, (3) severe orthopedic traumatic disease in the lower limbs, and (4) symptomatic decompensated heart failure. Moreover, the patients with more than moderate valvular heart disease were excluded from this study. Use of medications, including antihypertensive drugs, was kept constant during the study period. This study was approved by the local ethics committee of the involved institutions, and written informed consent was obtained from all participants.

As shown in the study protocol (Figure 1), all echocardiographic studies were performed within three days after RFCA (baseline) and at 3-6 months postoperatively (mid-term follow-up). Measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging/the American Society of Echocardiography.[4] LV ejection fraction (EF) and volumes were calculated by means of the modified biplane Simpson's method. LA volumes were measured at two time phases: when LA expanded to the maximum volume at end-systole (LAV_{max}) and when LA reduced its volume just after the booster-pump phase (LAV_{min}). As shown in Figure 2, the LA expansion index was calculated as $(LAV_{max} - LAV_{min}) \times 100/LAV_{min}$.[5] The transmitral early diastolic (E) and atrial wave (A) velocities were measured using pulsed-wave Doppler recordings.[6] Early diastolic (e') mitral annular velocity was measured using spectral tissue Doppler imaging with a sample volume placed at the septal and lateral mitral annulus, and the averaged value was calculated to estimate the LV filling pressure.[6] Stroke volume (SV) was measured at the LV outflow tract.

Speckle-tracking analysis was performed using dedicated software (TOMTEC-ARENA; TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany). The average values of the longitudinal strain from three LV apical views were calculated to obtain the LV global longitudinal strain (LV-GLS). As for the speckle-tracking analysis of the LA myocardium, LA-focused apical four- and two-chamber images were obtained. A predominant positive wave that peaked at LV systole was expressed as LA-GLS.[7]

For the preload stress test, commercially available LPP equipment (Dr Medomer DM-5000EX, Medo Industries Co, Ltd, Tokyo, Japan) was used. The LPP stress maneuver has been described previously in detail.[8,9] Briefly, it was designed to provide a continuous external pressure around both lower limbs using dedicated airbags at 90 mmHg pressure, which has been proven to safely provide an increase in cardiac preload.[9] Echocardiographic measurements were obtained both at rest and during LPP stress, and the changes in the measured parameters were calculated as the difference (Δ).

Electrical mapping and ablation were performed using the CARTO3 system (Biosense Webster, Diamond Bar, CA, USA) as a guide after the integration of a three-dimensional model of the anatomy of the LA and pulmonary veins obtained from pre-interventional computed tomography. RFCA was performed in a "point-by-point" manner, and the pulmonary veins were isolated by wide-area circumferential ablation. Patients were followed closely after RFCA and evaluated for recurrence at 3, 6, and 12 months during follow-up clinic visits. Procedural success was defined as freedom from documented AF lasting more than 30 seconds after the 3-month blanking period.[10]

Continuous variables were expressed as mean values and standard deviation for normally distributed data and as median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Independent sample *t*-test or Mann-Whitney *U* test was used to compare variables between groups. The paired *t*-test or Wilcoxon signed-rank test was used to compare differences in parameters between the two time-points, as appropriate. The initial univariate logistic regression analysis to identify univariate factors for identifying AF recurrence was followed by a multivariate analysis using a stepwise selection, with the *P*-value for entry into the model set at <0.10. All tests were two-tailed, and a *P*-value<0.05 was considered statistically significant. All analyses were performed using MedCalc version 16.5.0 (MedCalc Software; Ostend, Belgium).

Results

The baseline clinical characteristics of the 111 patients with AF are summarized in Table1. Approximately 50% of the patients had paroxysmal AF, and the remaining half had persistent or long-standing persistent AF. Hypertension was the most common comorbidity, followed by diabetes, heart failure, and stroke. The mean CHA_2DS_2-VASc score was 2.4±1.5. The baseline characteristics of the patients with paroxysmal and persistent AF are provided in the Supplementary Table.

During a median follow-up period of 14.2 (12.2-18.4) months, AF recurrence was observed in 23 patients, and the remaining 88 patients were allocated to the success group. Echocardiographic assessment was performed in AF rhythm in 3 patients at baseline and in 5 patients at the mid-term follow-up. For these cases, measurements were averaged from three non-consecutive beats with a cycle length within 10%-20% of the average heart rate.

No significant differences were observed between the groups in terms of age, CHA_2DS_2-VASc score, AF type, comorbidities, and laboratory data including brain natriuretic peptide level at baseline (Table 1). With respect to the hemodynamic and echocardiographic parameters, although the recurrence group was more likely to have larger LV volumes and LAVI and lower LVEF, there were no significant differences in LA functional parameters, including LA-GLS, LA stiffness index, and LA expansion index at baseline (Table 2).

During LPP stress, LV volume, LVEF, LAVI, E/e' ratio, and SVi significantly increased in both groups as a result of the increased preload (Table 2). Of note was that, although LA-GLS and LA expansion index significantly increased during LPP stress, these responses were blunted in the recurrence group. Consequently, the Δ LA expansion index was significantly larger in the success group at the baseline preload stress assessment (Table 2).

Follow-up echocardiography was performed at 6.1 (3.6-6.4) months after RFCA. As for LA parameters, LA-GLS, LAVI, and LA stiffness index all significantly improved at the mid-term follow-up after RFCA in the success group. Notably, the LA expansion index increased only in the success group (Table 2 and Figure 3). Moreover, LV structural and functional reverse remodeling was also observed at mid-term follow-up after RFCA, as evidenced by the improvement in LV-GLS, increase in e' velocity, and decrease in E/e' ratio only in the success group. Meanwhile, these beneficial effects of functional and structural reverse remodeling were blunted in the recurrence group (Table 2).

At the mid-term follow-up, the LA expansion index significantly increased during LPP stress in the success group, but not in the recurrence group (Table 2 and Figure 4). Together with the improvement in LA distensibility, SVi significantly increased during LPP stress without any elevation in LV filling pressure in the success group (Table 2 and Figure 4), indicating a significant improvement in the preload reserve. In contrast, in the recurrence group, the increased response of SVi was significantly blunted even at the expense of a significant increase in E/e' ratio during the LPP stress test (Table 2 and Figure 4).

The hazard ratios (HRs) and 95% confidence intervals (CI) for each baseline clinical, hemodynamic, and echocardiographic variables to predict AF recurrence are shown in Table 3. In a multivariate logistic regression analysis, although baseline LAVI and use of antiarrhythmic drugs were not selected as independent predictors of AF recurrence, LVEF and baseline ΔLA expansion index during LPP stress were selected as the independent determinants of AF recurrence after RFCA.

A receiver operating characteristic curve analysis identified the optimal cut-off value of LVEF to be 56.3%, and the ΔLA expansion index to be 13.7%, respectively (Figure 5).

Discussion

In the clinical course of AF, LA remodeling can be considered as time-dependent structural, functional, and electrical alterations.[1] These different types of LA remodeling are closely interrelated and progressively interact with each other,[11] resulting in alterations in the tissue architecture, including microscopic fibrotic remodelling[3] and macroscopic atrial dilatation. In these progressive pathological processes, LA fibrosis appears to play a central role in the development and maintenance of AF, by causing the heterogeneity of electrical conduction and a predisposition to re-entry.[2,3] Moreover, as the fibrotic burden increases, non-compliant LA would no longer be able to exert sufficient reservoir function; ultimately, LA acts as merely a passive conduit, that is LA fibrotic cardiomyopathy.[12,13] In this way, LA distensibility progressively deteriorates in parallel with LA myocardial fibrosis; therefore, LA reservoir function has recently gained attention for its clinical role in patients with AF. Khurram et al. studied 219 patients with AF referred to RFCA by analyzing LA pressure-volume loops and found that LA stiffness was a strong independent predictor of AF recurrence in patients undergoing RFCA.[14] Moreover, Hsiao et al. prospectively studied a total of 2,200 patients who complained of dyspnea and they clearly demonstrated that the echocardiographic LA expansion index was associated exponentially with the incidence of persistent AF.[5] These previous investigators underscored the importance that impaired resting LA distensibility was attributed to the development or recurrence of AF. Nevertheless, from a pathophysiological point of view, the stiffness characteristics of a chamber are not static, or dynamic capacity to distend itself in response to increased blood volume without increasing internal pressure. In this study, the baseline ΔLA expansion index could accurately predict AF recurrence presumably because the dynamic property of chamber distensibility could reflect the degree of LA myocardial fibrosis more accurately than static parameters.

In this study, not only a structural but a significant functional improvement in LA was observed after maintaining a sinus rhythm. These results may imply that the restoration of a sinus rhythm could not merely terminate the vicious cycle of electrical, structural, and functional remodeling, but reverse it. During the LPP stress test at the mid-term follow-up, the ΔLA expansion index dramatically improved in the success group, accompanied by an increased SV in response to the increased preload. These beneficial hemodynamic responses may suggest the restoration of the ability to reserve significant blood volume in the LA chamber without an elevation in LA pressure during the reservoir phase, consequently resulting in sufficient LV diastolic filling and increased SV. However, structural and functional reverse remodeling was not observed in the recurrence group. In this subgroup, it is speculated that the fibrotic burden of the LA myocardium might be too advanced to the extent that LA myocardial damage was no longer reversible. Therefore, the increased cardiac preload no longer properly reserved in the stiff LA. Instead, it merely led to an elevation in LA pressure, diastolic LV underfilling, and eventually reduced preload reserve.

Although RFCA is an established therapy for AF, its recurrence rate is reported to be 10-40% for paroxysmal AF and as high as 60-80% for persistent AF;[15] therefore, appropriate patient selection is a burning topic in this field. Theoretically, impaired LA distensibility would be closely related to the fibrotic burden; thus, patients with AF may undergo RFCA before the ΔLA expansion index is impaired for successful RFCA. The assessment of the ΔLA expansion index may be helpful in predicting patient outcomes, providing an appropriate strategy for RFCA, and making clinical decisions regarding post-procedural medical therapy.

This study has some limitations. First, because this study exclusively focused on the LA reservoir function, we were unable to assess other atrial functional parameters, including LA conduit and booster pump functions or right atrial function. Moreover, the pulmonary veins and their variations were not anatomically assessed in this study. Second, the LPP maneuver may not be available in all electrophysiological laboratories. Because passive leg-lifting stress is reported to be able to provide significant cardiac preload and can be used for the risk stratification of patients with heart failure,[16] further studies using this easy-to-use preload stress are expected to validate our findings.

In conclusion, the baseline ΔLA expansion index during LPP stress echocardiography was found to be a reliable marker to predict procedural success after RFCA. Moreover, maintaining the sinus rhythm has been shown to induce a virtuous cycle of LA reverse remodeling and improvement in preload reserve. These results may have substantial implications in appropriate patient selection, emerging therapies after RFCA, risk stratification, and postoperative follow-up.

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Figure legends

Figure 1. Study protocol

Transthoracic echocardiography and LPP stress echocardiography were performed within 3 days after RFCA (baseline) and at 3-6 months after RFCA (mid-term).

RFCA, radiofrequency catheter ablation; TTE, transthoracic echocardiography; LPP, leg-positive pressure.

Figure 2. Schematic presentation of the measurement of the LA expansion index

The LA expansion index was calculated as (LAV_{max} - LAV_{min}) × 100 / LAV_{min} both at rest and during LPP stress. Subsequently, the Δ LA expansion index was calculated by subtracing the expansion index at rest from that obtained during LPP stress. Moreover, the ΔLA expansion index was measured both at baseline and mid-term follow-up.

LA, left atrial; LAV, left atrial volume; LPP, leg-positive pressure.

Figure 3. Changes in resting LA functional and structural parameters from baseline to the mid-term follow-up after RFCA for both the success and recurrence groups

Each plot and bar represents mean and standard deviations.

LA, left atrium; RFCA, radiofrequency catheter ablation; GLS, global longitudinal strain; LAVI, left atrial volume index.

Figure 4. Changes in ΔLA expansion index and ΔSVi from baseline to the mid-term follow-up after RFCA in both success and recurrence groups

In the success group, both the ΔLA expansion index and ΔSVi significantly increased from baseline to the mid-term follow-up after RFCA, yet no significant changes were observed in the recurrence group.

LA, left atrium; SVi, stroke volume index; RFCA, radiofrequency catheter ablation.

Figure 5. ROC curve analysis for differentiating procedural success after RFCA

The baseline ΔLA expansion index was revealed to have a high discriminative potential for predicting procedural success after RFCA.

ROC, receiver operating characteristic; RFCA, radiofrequency catheter ablation; LA, left atrial.

Figure 1

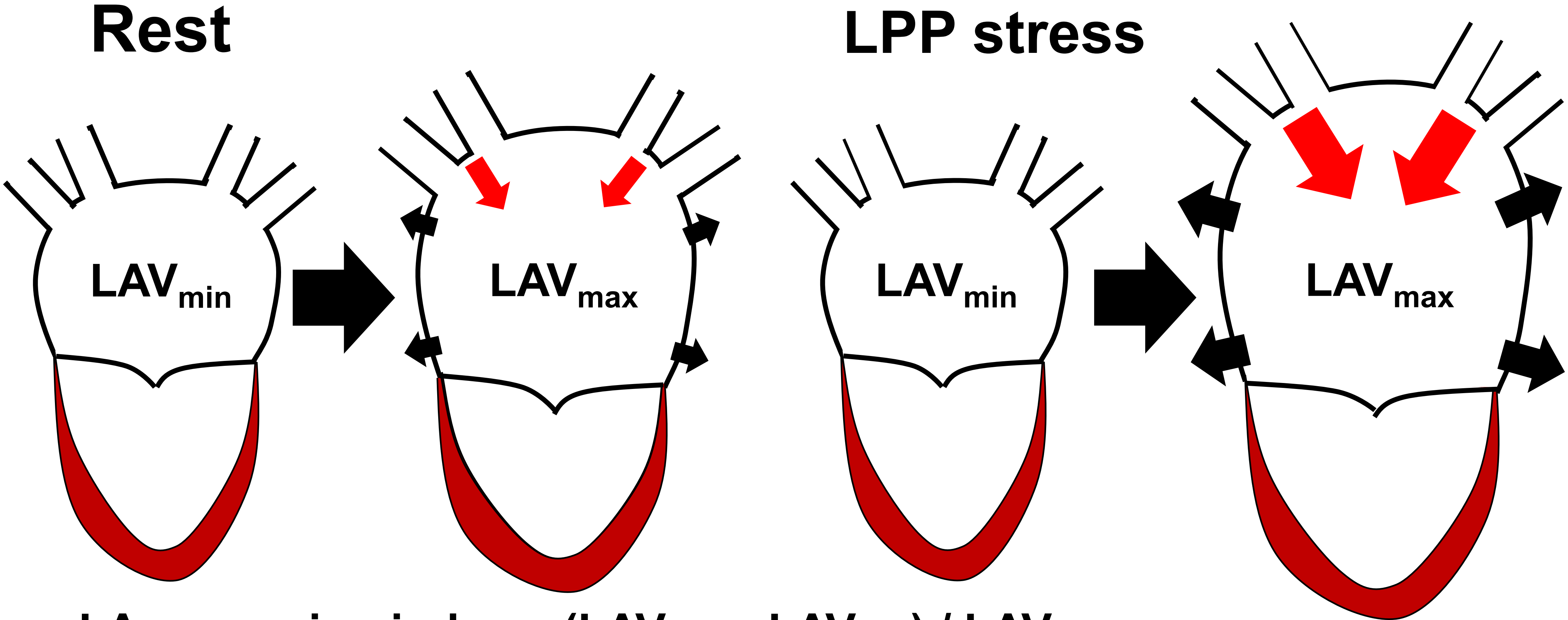
(A) (B) (C)

Catheter ablation
- ✓ Laboratory examination

Baseline
- ✓ Immediately after catheter ablation
- ✓ TTE : rest + LPP

Mid-term follow-up
- ✓ 3-6 months after catheter ablation
- ✓ TTE : rest + LPP

Figure 2



LA expansion index = $(LAV_{max} - LAV_{min}) / LAV_{min}$
Δ LA expansion index = $\text{expansion index}_{LPP} - \text{expansion index}_{Rest}$

Figure 3

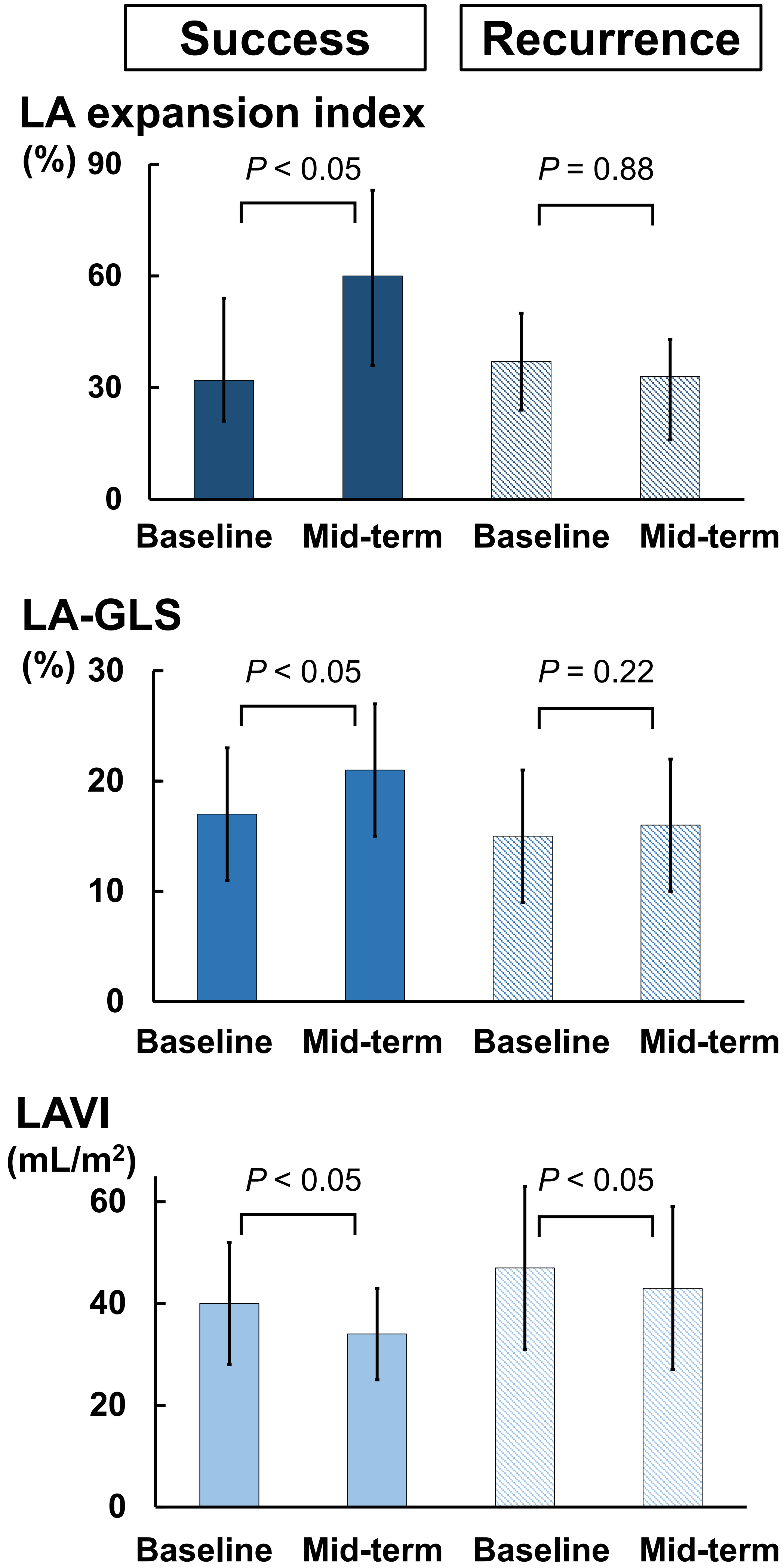
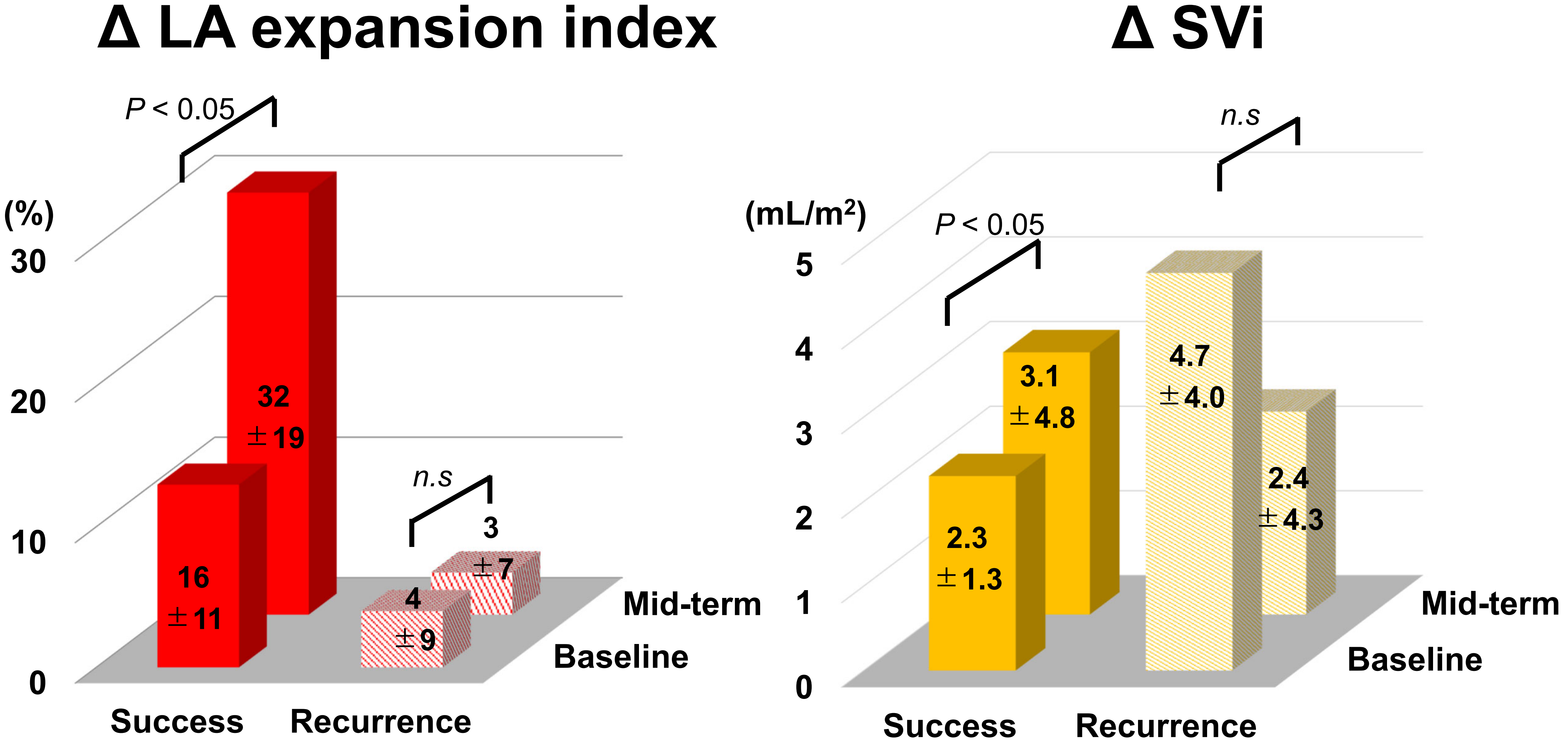
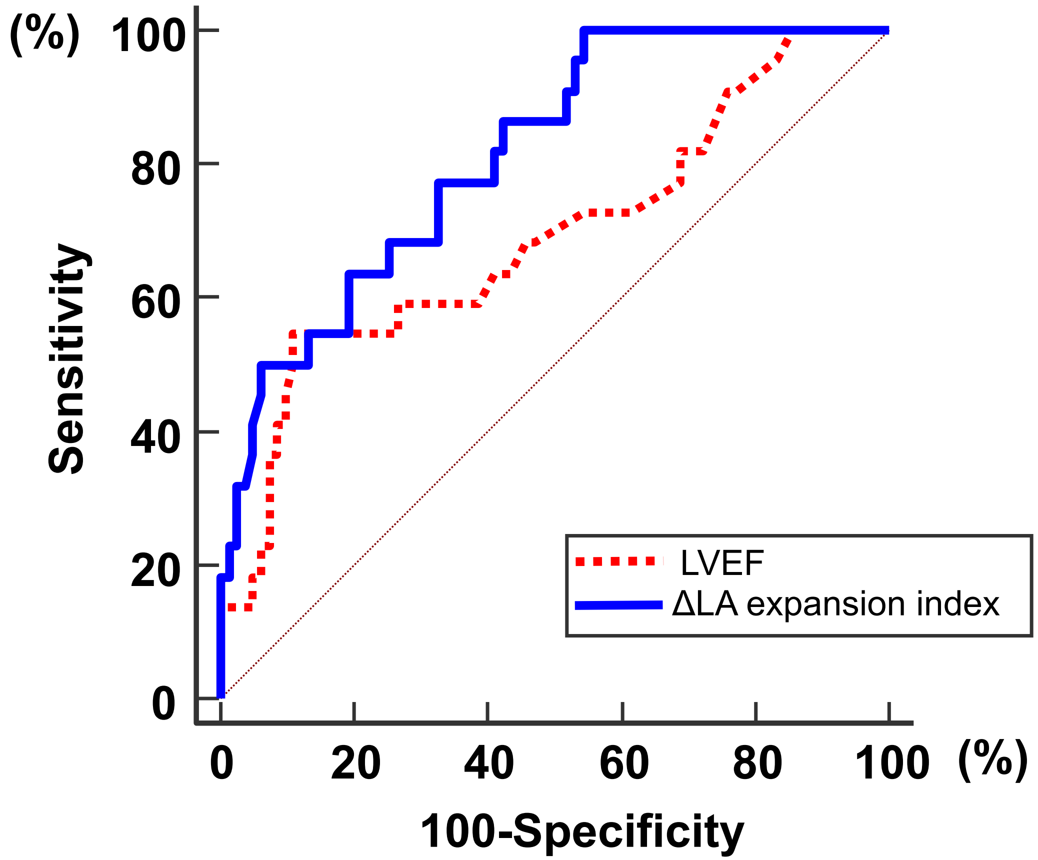

Success
Recurrence
LA expansion index
(%)
90
60
30
0
P < 0.05
P = 0.88
Baseline
Mid-term
Baseline
Mid-term
LA-GLS
(%)
30
20
10
0
P < 0.05
P = 0.22
Baseline
Mid-term
Baseline
Mid-term
LAVI
(mL/m²)
60
40
20
0
P < 0.05
P < 0.05
Baseline
Mid-term
Baseline
Mid-term

Figure 4



Δ LA expansion index
P < 0.05
(%)
30
20
10
0
32
±19
16
±11
n.s
3
±7
4
±9
Mid-term
Baseline
Success
Recurrence
Δ SVi
n.s
(mL/m²)
P < 0.05
5
4
3
2
1
0
3.1
±4.8
2.3
±1.3
4.7
±4.0
2.4
±4.3
Mid-term
Baseline
Success
Recurrence

Figure 5



	Cut-off	ACU (95% CI)	Sensitivity	Specificity	*P* value
LVEF (%)	56.3	0.663	52.2	88.6	<0.05
Baseline ΔLA expansion index	13.7	0.813	100	45.8	<0.001

Table1. Baseline clinical characteristics of the patients with atrial fibrillation

Variables	All patients (N = 111)	Success (N = 88)	Recurrence (N = 23)	*P*-value
Age (years)	67±9	67±10	67±8	0.97
Body mass index (Kg/m^2)	25±4	25±4	24±3	0.54
Body surface area, (m^2)	1.7±0.2	1.7±0.2	1.7±0.2	0.69
CHA_2DS_2-VASc score	2.4±1.5	2.3±1.5	2.6±1.4	0.42
Types of Atrial Fibrillation				
Paroxysmal	58 (52%)	49 (56%)	9 (39%)	0.16
Persistent/Long-standing persistent	53 (48%)	39 (44%)	14 (61%)	0.18
Comorbidities				
Heart failure	12 (11%)	7 (8%)	5 (22%)	0.06
Hypertension	65 (59%)	55 (63%)	10 (43%)	0.10
Diabetes	29 (26%)	24 (27%)	5 (22%)	0.70
Stroke	12 (11%)	9 (10%)	3 (13%)	0.70
Laboratory data				
Hemoglobin (g/dL)	13±1	13±1	13±2	0.76
Creatinine (mg/dL)	0.9±0.2	0.9±0.2	0.9±0.2	0.37
Estimated glomerular filtration rate (mL/min/1.73m^2)	65±13	65±13	61±12	0.17
Brain natriuretic peptide (pg/mL)	76 (31-141)	58 (29-144)	108 (75-138)	0.22

Data are presented as n, mean ± SD, n (%), or median (interquartile range).

Table 2. Comparisons of haemodynamic and echocardiographic parameters during leg-positive pressure stress both at baseline and mid-term follow-up

	Success				Recurrence			
	Baseline		Mid-term follow up		Baseline		Mid-term follow up	
Variable	Rest	Leg-positive pressure	Rest	Leg-positive pressure	Rest	Leg-positive pressure	Rest	Leg-positive pressure
Hemodynamics								
Systolic blood pressure (mmHg)	126±18	129±19*	124±20	123±17	127±18	124±14	120±21	121±18
Diastolic blood pressure (mmHg)	73±14	76±14*	67±16†	68±14	74±9	72±18	68±21	70±17
Heart rate (bpm)	71±13	69±10*	67±10†	64±9*	71±15	69±12*	66±14	65±18
Stroke volume index (mL/m^2)	39±11	42±12*	37±9†	41±10*	42±11	46±12*	36±7†	40±8*
ΔStroke Volume index (mL/m^2)	2.3±1.3		3.1±4.8†		4.7±4.0		2.4±4.3‡	
Echocardiographic indices								
Left ventricular volume index (mL/m^2)								
End-diastole	47±10	51±11*	47±12	54±14*	56±12‡	61±16*	52±15	59±15*
End-systole	17±5	18±5	18±6	20±7*	24±10‡	25±12	21±8‡	22±10
Left ventricular mass index (g/m^2)	86±27		82±21†		95±23		97±27‡	
Left ventricular ejection fraction (%)	63±6	65±5*	63±5	65±5*	58±9‡	61±11	60±8	65±8*
Left atrial volume index (mL/m^2)	40±12	45±13*	34±9†	40±10*	47±16‡	52±17*	43±16†‡	48±18*
E/A ratio	1.6 (1.1-2.2)	1.5 (1.2-2.4)	1.2 (0.9-1.6)†	1.3 (1.0-1.6)*	1.9 (1.5-2.5)	2.0 (1.5-2.5)	1.5 (1.0-2.2)†	1.5 (1.2-1.8)
e' velocity (cm/sec)	7.3±1.7	7.6±2.0*	7.4±1.7†	7.6±1.7	7.6±2.0	7.6±2.1	7.5±2.3	7.2±2.6
E/e' ratio	11±3	13±5*	10±3†	11±4	12±5	13±5*	11±4	14±10*

ΔE/e’ ratio	1.2±2.1		1.0±2.2		1.5±2.3		3.4±7.5‡	
Tricuspid regurgitation-pressure gradient (mmHg)	23±9	24±8	19±9†	22±9*	25±7	24±8	21±10	22±10
Tricuspid annular plane systolic excursion (mm)	22±4	23±4	22±4	23±4*	23±4	24±5	22±4	24±5
Inferior vena cava diameter (mm)	14±4	16±4*	12±4†	14±3*	14±4	15±3	12±3†	14±3*
Left ventricular-global longitudinal strain (%)	13±4	13±4	15±4†	15±4	12±3	13±3	13±5	13±5
Left atrial-global longitudinal strain (%)	17±6	19±5*	21±6†	23±7*	15±6	16±6*	16±6‡	17±5
Left atrial expansion index (%)	40±27	56±28*	61±30†	93±34*	37±14	40±14*	34±17	36±18*
ΔLeft atrial expansion index (%)	16±11		32±19†		3.7±9.0‡		2.6±6.5‡	

**P*<0.05 vs. rest, †*P*<0.05 vs. baseline, ‡*P*<0.05 vs. success

Data are presented as n, mean ± SD, n (%), or median (interquartile range).

Table 3. Univariate and multivariate logistic regression analysis to predict AF recurrence

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Clinical variables						
Age (y)	0.999	0.952-1.049	0.97			
Gender (male)	0.857	0.314-2.340	0.76			
CHA_2DS_2-VASc score	1.120	0.821-1.528	0.47			
Type of atrial fibrillation (paroxysmal)	0.512	0.201-1.306	0.16			
Brain natriuretic peptide concentration, pg/mL	1.001	0.997-1.004	0.73			
Radiofrequency catheter ablation strategy (pulmonary vein isolation)	1.159	0.630-2.131	0.64			
Prescription of antiarrhythmic drugs	3.301	1.233-8.838	<0.05			
Baseline echocardiographic variables						
Left ventricular ejection Fraction (%)	0.906	0.847-0.968	<0.01	0.900	0.831-0.974	<0.05
Left atrial volume index (mL/m^2)	1.040	1.004-1.077	<0.05			
E/e’ ratio	1.022	0.899-1.161	0.74			
Left ventricular-global longitudinal strain (%)	0.928	0.814-1.058	0.26			
Left atrial-global longitudinal strain (%)	0.923	0.818-1.042	0.19			
Left atrial expansion index (%)	0.994	0.974-1.014	0.58			
Variables under leg-positive pressure stress						
ΔLeft atrial expansion index (%)	0.831	0.754-0.915	<0.001	0.900	0.753-0.931	<0.001

HR, hazard ratio; CI, confidential interval.

All other abbreviations as in Table 1 and 2.