Effects of Radiofrequency Catheter Ablation on Cardiac Reserve Using Preload Stress Echocardiography in Paroxysmal and Persistent Atrial Fibrillation

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The effects of catheter ablation on exercise tolerance and quality of life in patients with atrial fibrillation (AF) have been reported. We assessed cardiac function in more detail using the leg positive pressure (LPP) technique and found that contractile reserve is particularly important in relation to exercise tolerance and prognosis. In this study, we used the LPP technique to examine changes in contractile reserve immediately after ablation and 6 months later. We prospectively enrolled patients who underwent catheter ablation for AF at 2 institutes. We performed LPP stress echocardiography 2 to 3 days after (FU-1) and 6 months after (FU-2) ablation to examine changes in cardiac function indexes. The primary end point was improvement in contractile reserve. Ultimately, 109 patients (mean age 67.4 ± 9.6 years; 70% men) underwent 2 sessions of LPP stress echocardiography. The median CHA_2DS_2-VAS_C score was 2 (interquartile range 13). From FU-1 to FU-2, the change in the stroke volume index after the LPP maneuver increased in patients with paroxysmal and persistent AF with low CHA_2DS_2-VAS_C scores (both $p < 0.05$). Regardless of AF subtype, contractile reserve at FU-2 improved in patients with low CHA_2DS_2-VAS_C scores compared with that at FU-1. In contrast, patients with high CHA_2DS_2-VAS_C scores had no change. In conclusion, patients with AF with a low CHA_2DS_2-VAS_C score had improved contractile reserve after ablation, whereas patients with high scores did not show any improvement. Aggressive interventions in patients with high scores may lead to better management after catheter ablation. **(Am J Cardiol 2021;00:1−7)**

Recent trials have shown that radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) is superior to antiarrhythmic drugs for decreasing recurrence, prolonging the time in sinus rhythm, and improving patient quality of life.[1,2] However, theories regarding changes in cardiac function after RFCA remain controversial. Recently, we used preload stress echocardiography with leg positive pressure (LPP) to assess echocardiographic variables during preload augmentation for the detailed assessment of cardiac function. In our previous studies, cardiac response (change in stroke volume) during preload augmentation was an important part of the phenomenon in the evaluation of prognosis and exercise capacity in various cardiovascular diseases.[3,4] Thus, we hypothesized that RFCA for AF would change the cardiac reserve assessed by preload stress echocardiography and that changes would be linked to subtypes of AF. The purpose of this study was to compare the changes in cardiac reserve assessed by preload stress echocardiography in patients who underwent RFCA for paroxysmal AF (PAF) and persistent AF (PerAF).

Methods

We designed a multicenter prospective study to assess cardiac functional recovery in patients with AF after RFCA. We enrolled 139 patients with PAF or PerAF who underwent RFCA for AF from October 2018 to March 2020 at 2 different cardiovascular centers: Tokushima University Hospital and Kobe University Hospital. All participants underwent preload stress echocardiography. The exclusion criteria of the study were (1) lack of baseline data, (2) incomplete echocardiographic examination due to pain or sickness, and (3) AF rhythm was measured at the first LPP echocardiography because of difficulty assessing and comparing cardiac function due to a lack of atrial contraction and irregular heart rhythm in patients with AF. In

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See page 6 for disclosure information.

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the analysis of follow-up data, we also excluded patients who were lost to follow-up and who had an AF rhythm at follow-up. The study was reviewed and approved by the Institutional Review Board of all the involved institutions.

Echocardiography was performed before ablation, 2 to 3 days after RFCA (FU-1), and 6 months after RFCA (FU-2), using commercially available ultrasound machines. Measurements and recordings were obtained according to the American Society of Echocardiography recommendations.[5] All strains were analyzed offline using vendor-independent speckle tracking software (EchoInsight, Epsilon Imaging, Ann Arbor, Michigan). Global longitudinal strain was obtained by averaging all segmental strain values from the apical 4-chamber, 2-chamber, and long-axis views. Left atrial (LA) pump, conduit, and reservoir strain were averaged from the apical 4-chamber and 2-chamber views.[6] Written informed consent was obtained from all the patients before ablation. Preload stress echocardiography was performed at FU-1 and FU-2 but not before ablation because of the AF rhythm measured during echocardiography. To compare stable measurements taken in sinus rhythm, FU-1 and FU-2 were compared, rather than using measurements taken before ablation. For the preload stress test, commercially available LPP equipment (Leg Compression System, Corona Industries LTD, Tokushima, Japan) was used. The procedure of the LPP stress maneuver was described in detail previously.[7] Briefly, it was designed to provide a continuous external pressure around both lower limbs using dedicated airbags at 90-mm Hg pressure. This pressure was proven to safely provide an effective increase in ventricular preload with evidence based on the findings from an invasive hemodynamic study. Echocardiographic measurements were obtained at rest and during LPP stress. All LPP stress echocardiographic examinations were performed 20 seconds after the inflation of the airbags. The primary outcome of our study was the change in stroke volume index (SVi) during the LPP stress maneuver as a marker of contractile reserve. Pulmonary vein isolation was performed mainly for PAF. An additional nonpulmonary vein trigger ablation was performed if AF was initiated by trigger activity from a nonpulmonary vein focus. Additional substrate modifications were performed in patients with PAF if the operator considered noninducibility more important than trigger focus elimination. Pulmonary vein isolation and box isolation were performed mainly for PerAF.

Comparisons between groups (before ablation, FU-1 and FU-2) were performed with either a paired *t* test or repeated measures analysis of variance. Categorical variables are presented as numbers and percentages. Comparisons between groups were performed with Cochran's Q test and the McNemar test. For the analysis of contractile reserve, we divided the study cohort into 4 groups according to the CHA_2DS_2-VAS_C score and type of AF. Because the CHA_2DS_2-VAS_C score is primarily a tool for assessing the risk of stroke in patients with AF, we used this scoring system as a surrogate for co-morbidity burden in our analysis. The change in cardiac contractile reserve, represented by the change in SVi during LPP, was compared between FU-1 and FU-2 using either the Welch *t*-test or Wilcoxon signed-rank test according to the results of the *F* test and Kolmogorov-Smirnov test. The inferior vena cava collapsibility indexes were used to estimate RAP. Systemic vascular resistance (SVR) was calculated as SVR = (mean arterial pressure − right atrial pressure)/cardiac output. The statistical analyses were performed using standard statistical software packages, EZR (version 1.41, Saitama Medical Centre, Jichi Medical University, Saitama, Japan) and MedCalc Software 19.0.6 (Mariakerke, Belgium). p Values <0.05 were considered to indicate statistical significance.

Results

Figure 1 shows the patient flow diagram. A total of 133 patients with AF after RFCA who underwent first preload stress echocardiography were included in the study (Table 1). The median CHA_2DS_2-VASc score was 2

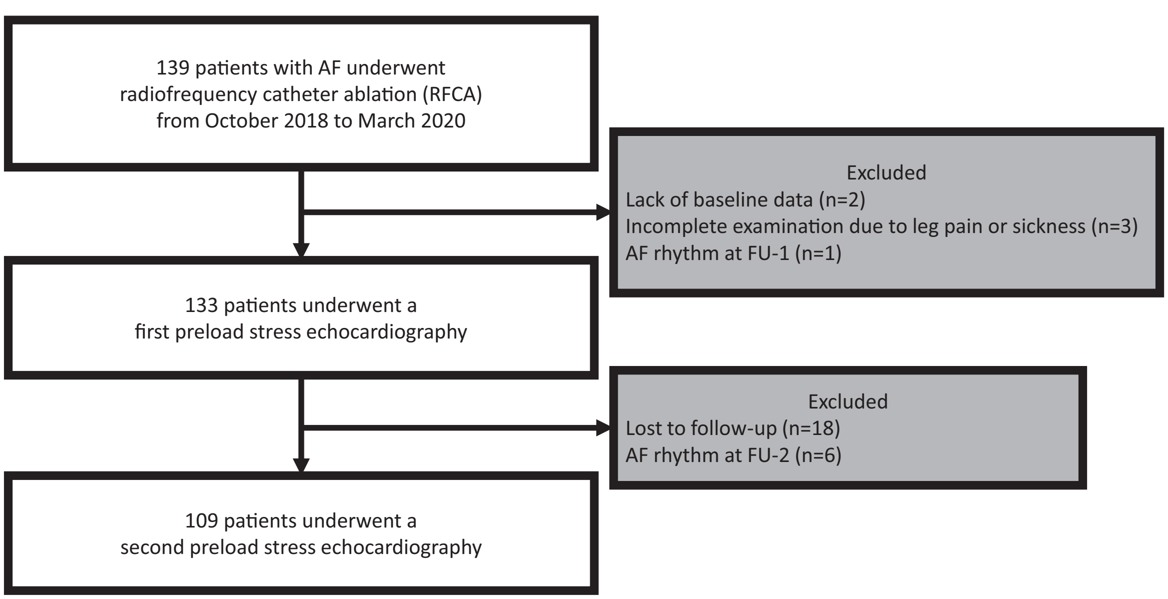

Figure 1. Flow chart of patient recruitment.

Table 1
Clinical characteristics

Variable	All (n=133)
Age (yr)	67±9
Men	97 (73%)
Height (cm)	164±9
Body weight (kg)	67±14
Body surface area (m^2)	1.68±0.2
Body mass index (kg/m^2)	25±4
Heart failure	13 (10%)
Coronary heart disease	11 (8%)
Diabetes mellitus	21 (16%)
Hypertension	77 (58%)
Stroke	16 (12%)
Current smoker	11 (8%)
Paroxysmal AF	70 (53%)
Persistent AF	63 (47%)
Rhythm at pre-ablation	
Sinus rhythm	72 (54%)
AF/AFL rhythm	61 (46%)
Procedure	
PVI	60 (45%)
PVI + box isolation	73 (55%)
Laboratory data	
Hemoglobin (g/dL)	13±1
Estimated glomerular filtration rate (mL/min/1.73 m^2)	64±14
C-reactive protein (mg/dL)	0.14±0.50
Brain natriuretic peptide (pg/dL)	76 (29-140)

Data are presented as the number of patients (percentage), mean ± SD or median (interquartile range).

Table 2
Changes in echocardiographic parameters immediately after ablation and at 6-month follow-up

Variable	Pre-ablation	FU-1	FU-2
Hemodynamics			
Systolic blood pressure (mmHg)	128±21	127±18	122±21
Diastolic blood pressure (mmHg)	78±14	73±13*	66±17*,†
Heart rate (bpm)	73±19	70±13	66±11*,†
Stroke volume index (mL/m^2)	38±15	41±11	38±9
Systemic vascular resistance (wood)	23±8	20±13	20±6
Echocardiographic indices			
Left ventricular end-diastolic volume index (mL/m^2)	50±14	50±12	50±13
Left ventricular end-systolic volume index (mL/m^2)	21±9	19±7*	19±7*
Left ventricular ejection fraction (%)	59±8	62±7*	62±6*
Left atrial volume index (mL/m^2)	43±16	41±14	35±11*,□
Tricuspid regurgitation pressure gradient (mmHg)	21±6	22±7	20±9†
Inferior vena cava max (mm)	13±4	14±4	12±4*,†
Early diastolic transmitral flow velocity (cm/s)	80±19	81±20	72±19*,†
Late diastolic transmitral flow velocity (cm/s)	67±27	52±20	59±19†
Early diastolic transmitral flow velocity / late diastolic transmitral flow velocity ratio	1.3±0.5	1.8±0.9*	1.3±0.5†
Mean early diastolic mitral annular motion (cm/s)	8±3	7±2*	7±2*
Early diastolic transmitral flow velocity / early diastolic mitral annular motion ratio	12±7	12±4	11±4
Mitral valve regurgitation			
None	94 (71%)	101 (76%)	90 (82%)*
Mild	38 (29%)	32 (24%)	18 (17%)*
Moderate	1 (1%)	0	1 (1%)
Severe	0	0	0

Data are presented as number of patients (percentage), mean ± SD.
P <0.05.
* vs pre-ablation, P <0.05.
† vs FU-1.

(interquartile range [IQR] 1 to 3). To analyze the changes in echocardiographic data, after the exclusion of illegible patients, 109 patients underwent a second preload stress echocardiography procedure. The basic clinical backgrounds of these 109 patients were similar to those measured before exclusion (median CHA_2DS_2-VASc score 2; IQR 1 to 3). The median duration of follow-up was 6.2 months (IQR 3.8 to 6.5 months). To assess acute changes after RFCA, we compared the echocardiographic parameters measured before and 2 to 3 days after RFCA (FU-1). Before RFCA, 72 patients (54%) who underwent echocardiography had sinus rhythm, whereas 61 patients (46%) had AF rhythm. At FU-1, all patients who underwent echocardiography had sinus rhythm. To assess cardiac remodeling and functional recovery after RFCA, we compared the echocardiographic parameters between FU-1 and FU-2 (Table 2). Regarding LV function, there were no differences in left ventricular ejection fraction (LVEF) and LV sizes between FU-1 and FU-2. Global longitudinal strain also did not change at FU-2 (−14.9 ± 4.0 vs −15.5 ± 3.1, p = 0.17). Regarding LA function, LA volume index (LAVI) decreased at FU-2. LA pump strain improved at FU-2 (−5.9 ± 5.0 vs −8.6 ± 5.1, p <0.01). Regarding Doppler parameters, e′ and E/e’ did not change at FU-2. The E/A ratio was reduced because of increases in the transmitral flow velocity-A wave. Thus, LA functional recovery occurred at FU-2.

To check the hemodynamic response to preload augmentation among patients by clinical characteristics, we divided our cohort into 4 groups stratified by type of AF and CHA_2DS_2-VAS_C score (group 1: PAF with low CHA_2DS_2-VAS_C score [<2], group 2: PAF with high $CHA_2DS_2VAS_C$ score [≥2], group 3: PerAF with low CHA_2DS_2-VAS_C score [<2], and group 4: PerAF with high CHA_2DS_2-VAS_C score [≥2]) (Table 3). At FU-2, 5 patients had recurrent AF, but there was no difference in recurrence among any of the groups (group 1, n = 0, 0%; group 2, n = 2, 5%; group 3, n = 2, 12%; group 4, n = 1, 3%). Regarding the LV data, there was no difference in ΔLVEF and Δ E/A, Δ E/e′ (i.e., changes during the LPP procedure) between FU-1 and FU-2 in any of the groups. The group with the largest effect on LV volumes had PAF with an elevated CHA_2DS_2-VAS_C score. Concerning the LA data, there was also no significant difference in ΔLAVI (i.e., the change in LAVI during the LPP procedure) between FU-1 and FU-2 in any of the groups. Regarding the RV data, there was no significant difference in Δ tricuspid regurgitant pressure gradient and Δinferior vena cava max (i.e., the changes during the LPP procedure) between FU-1 and FU-2 in all the groups. Interestingly, the change in SVi during the LPP procedure (i.e., ΔSVi as a marker of LV contractile reserve) was improved at FU-2 in patients with PAF and PerAF, especially in those with a low CHA_2DS_2-VAS_C score (i.e., groups 1 and 3). The changes in ΔSVi are shown in Figure 2. From FU-1 to FU-2, ΔSVi increased in groups 1 and 3, with this increase appearing to be greater in group 1 than in group 3. In contrast, there was no change in ΔSVi in groups 2 and 4 who had high

Table 3
Changes in functional reserve at 6-month follow-up

	Paroxysmal atrial fibrillation						Persistent atrial fibrillation					
	CHA_2DS_2-VASC<2			CHA_2DS_2-VASC≥2			CHA_2DS_2-VASC<2			CHA_2DS_2-VASC≥2		
	Group 1 (n=19)			Group 2 (n=40)			Group 3 (n=17)			Group 4 (n=33)		
	FU-1	FU-2	*P* value	FU-1	FU-2	*P* value	FU-1	FU-2	*P* value	FU-1	FU-2	*P* value
ΔStroke volume index (mL/m^2)	2±5	6±4	0.01	3±6	4±5	0.24	1±3	4±4	0.03	4±5	4±5	0.95
ΔLeft ventricular end-diastolic volume index (mL/m^2)	4±7	7±5	0.19	3±10	8±10	0.03	6±10	10±10	0.37	6±6	6±9	0.80
ΔLeft ventricular end-systolic volume index (mL/m^2)	0±3	2±4	0.08	0±4	2±5	0.04	1±6	4±5	0.17	1±4	1±4	0.68
ΔLeft ventricular ejection fraction (%)	3±6	1±5	0.27	0±11	2±5	0.18	4±7	1±5	0.20	2±6	3±4	0.58
ΔLeft atrial volume index (mL/m^2)	6±9	5±6	0.67	3±8	3±7	0.70	1±10	3±6	0.52	3±14	2±11	0.69
ΔTricuspid regurgitation pressure gradient (mmHg)	1±3	3±5	0.12	3±5	2±3	0.38	0±8	4±6	0.08	2±7	2±3	0.66
ΔInferior vena cava max (mm)	3±3	2±2	0.42	2±3	2±2	0.79	2±3	1±3	0.85	2±3	2±2	0.21
ΔEarly diastolic transmitral flow velocity / late diastolic transmitral flow velocity ratio	0.0±0.2	0.2±0.3	0.15	0.0±0.4	0.1±0.3	0.23	0.1±0.5	0.1±0.2	0.84	0.0±0.8	0.1±0.3	0.40
ΔEarly diastolic transmitral flow velocity / early diastolic mitral annular motion ratio	2±6	0±3	0.37	0±2	1±2	0.27	0±2	0±3	0.83	1±4	0±3	0.22

Delta means the change during the LPP procedure.

CHA_2DS_2-VAS_C scores. According to these results, the LV contractile reserve was improved at FU-2, especially in patients with a low CHA_2DS_2-VAS_C score. Figure 3 shows representative cases of patients with AF with either a low or high CHA_2DS_2-VAS_C score. In the patient with a low CHA_2DS_2-VAS_C score, ΔSVi increased from FU-1 to FU-2. Therefore, in the patient with a high CHA_2DS_2-VAS_C score, there was no increase in ΔSVi. We also compared the change

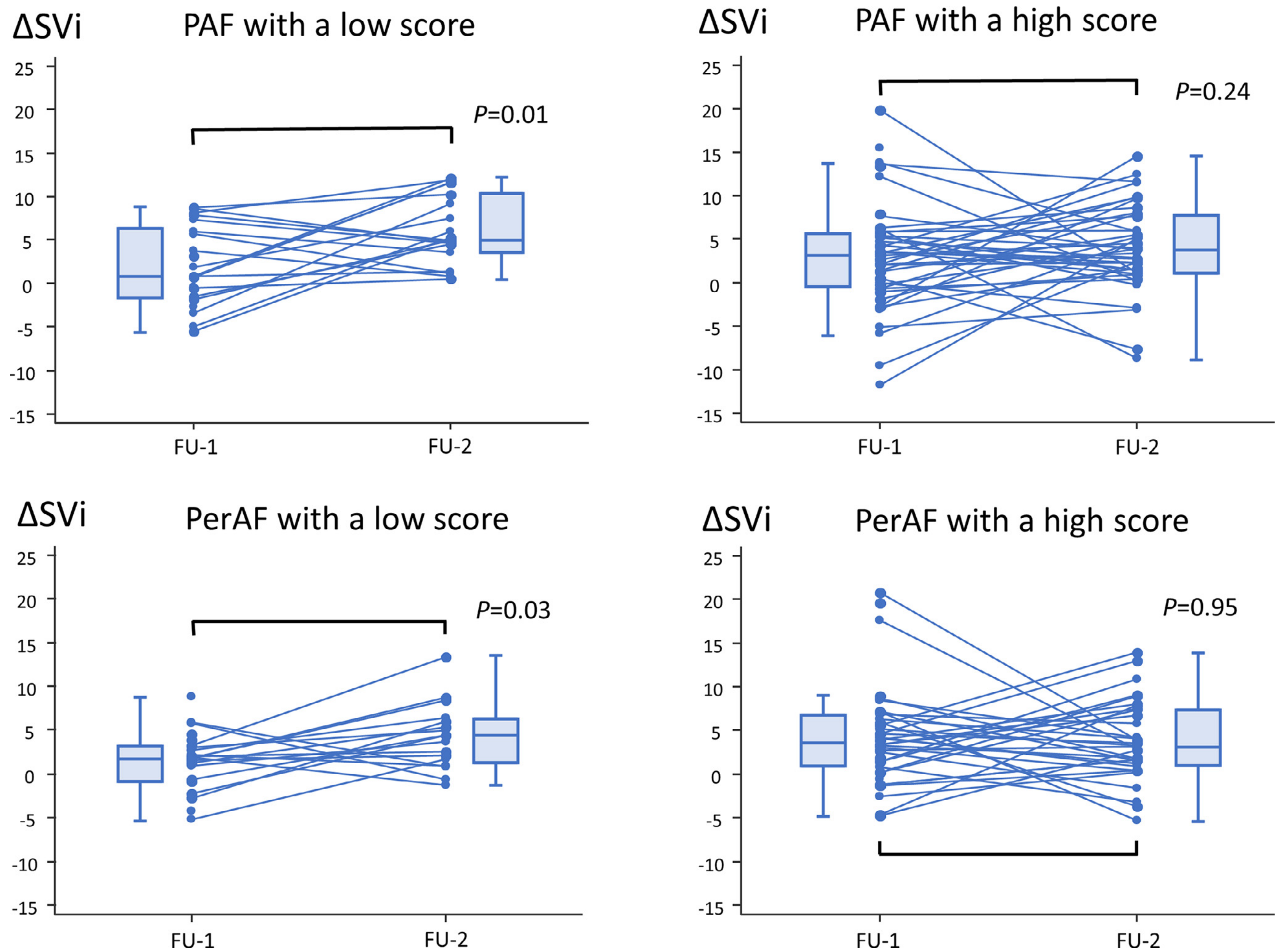

Figure 2. Change in ΔSVi reflecting cardiac reserve. From FU-1 to FU-2, ΔSVi increased in group 1 and group 3, and ΔSVi in group 1 appeared to increase more than that in group 3. In contrast, there was no change in group 2 and group 4.

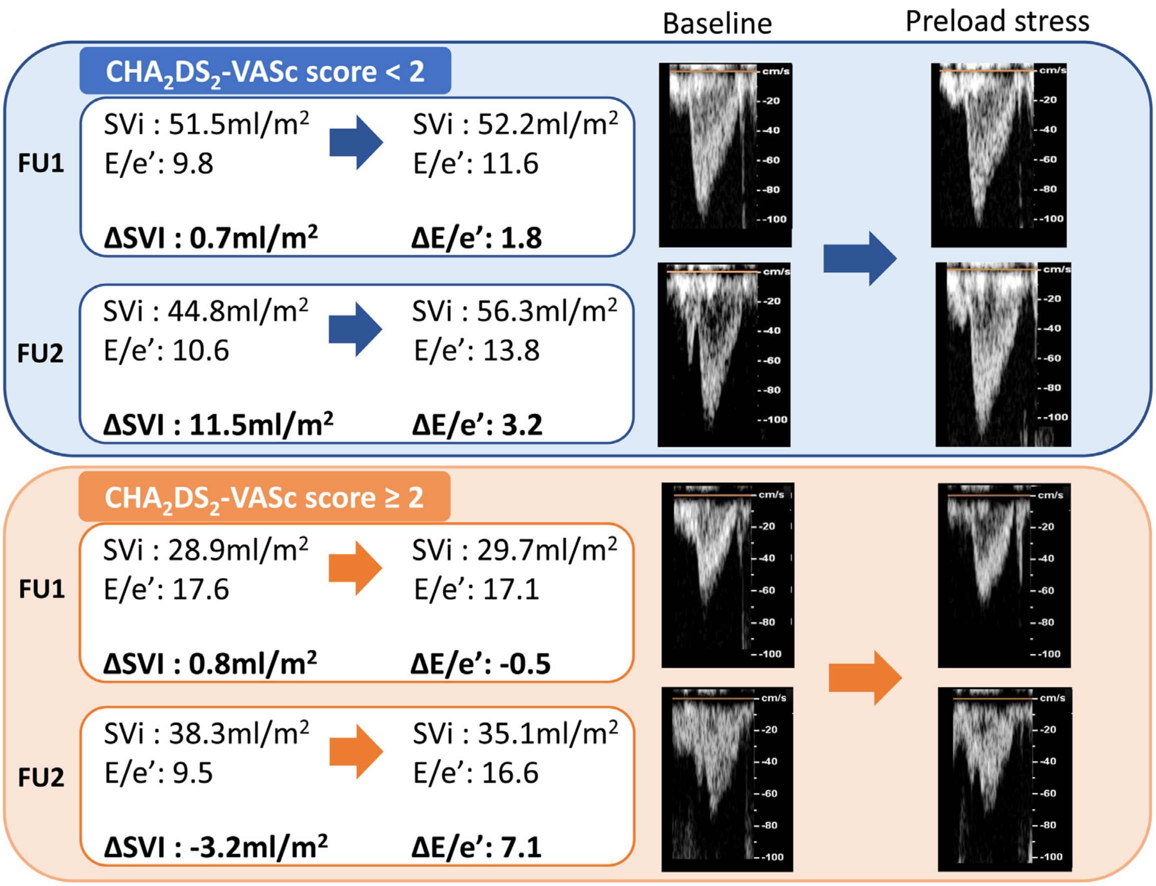

Figure 3. Representative cases of patients with AF with either a low CHA_2DS_2-VAS_C score or high CHA_2DS_2-VAS_C score. ΔSVi increased between FU-1 and FU-2 in the patient with a low CHA_2DS_2-VAS_C score.

in ΔSVi from FU-1 to FU-2 between the groups with either a low or high $CHA_2DS_2VAS_C$ score. The change in ΔSVi was greater in the group with a low CHA_2DS_2-VAS_C score than in the group with a high score (3.4 ± 5.5 vs 0.8 ± 7.5, p = 0.04).

The measurements were performed in a group of 20 randomly selected patients by 1 observer and then repeated on 2 separate days by 2 observers. Reproducibility of the measurements was expressed as the mean percentage error (absolute difference divided by the average of 2 observations). There was good intraobserver and interobserver variability for the SVi measurement (5.4 ± 5.0% and 6.0 ± 6.1%), LVEF (4.5 ± 1.8% and 5.1 ± 2.9%), LV end-diastolic volume (6.1 ± 3.1% and 7.3 ± 5.1%), LAVI (6.0 ± 4.2% and 6.2 ± 4.5%), E wave (7.7 ± 6.2% and 8.1 ± 6.1%), and A wave (5.2 ± 3.8% and 5.3 ± 3.8%), respectively.

Discussion

The objective of our study was to assess the change in contractile reserve in patients with PAF and PerAF after RFCA, measured by preload stress echocardiography immediately after RFCA and 6 months later. The study provides new insights into changes in cardiac function after RFCA: (1) LVEF improved slightly immediately after RFCA; (2) LA functional parameters were improved 6 months after RFCA; and (3) contractile reserve improved, especially in patients with low CHA_2DS_2-VASc scores. Our data suggested that contractile reserve improved immediately after RFCA and was maintained for a least 6 months in patients with AF who had a low CHA_2DS_2-VAS_C score.

Recently, we showed that contractile reserve is a sensitive marker of cardiac functional parameters in patients with heart failure with reduced ejection fraction,[8] and that impaired contractile reserve occurs in patients with heart failure with preserved ejection fraction.[9] These studies reported that an increase in SVi after the LPP procedure was associated with a better prognosis. In patients with a good prognosis, SVi increased about 5 ml/m^2 after the LPP procedure. In the present study, we defined an increase in SVi after the LPP procedure as contractile reserve and examined changes in this reserve after RFCA. During the 6-month follow-up, contractile reserve (ΔSVi) improved by approximately 5 ml/m^2 in patients with AF and a low CHA_2DS_2-VAS_C score. Our finding of changes in SVi is consistent with those of previous reports. To investigate the mechanism that was potentially involved in the change in ΔSVi (i.e., which preload or afterload parameter affected this change), we assessed SVR as an index of afterload and E/e′ as an index of preload. During the LPP procedure, E/e' increased (11 ± 3 to 12 ± 5, p = 0.03), whereas SVR did not change significantly (20 ± 13 to 19 ± 6, p = 0.42). Therefore, LPP is mainly a procedure for increasing the preload. In addition, ΔSVi showed an association with Δ E/e′ (r = 0.25, p = 0.01) but not with ΔSVR (r = −0.18, p = 0.07). Taken together, these results indicate that the change in SVi in our study cohort was influenced mainly by an increase in preload.

It is well known that CHA_2DS_2-VAS_C scores are associated with poor outcomes (recurrence of AF, death, stroke, and heart failure hospitalization) after RFCA.[10,11] Because contractile reserve is associated with exercise tolerance and prognosis in the heart failure population, there may be a link between impaired contractile reserve and poor prognosis backgrounds. There is no evidence of treatment for contractile reserve in the clinical setting. Our data suggested that RFCA can improve the contractile reserve during preload stress in the PAF cohort and the PerAF cohort with a low-risk score. This finding may be a consequence of these patients having a lower incidence of diabetes, vascular disease, and hypertension, and less myocardial fibrosis, microvascular damage, and cardiac remodeling. In contrast, it is difficult to explain why the contractile reserve did not improve in the cohort with high-risk scores. There are several reports of improvement in cardiac function after ablation in patients with both systolic and diastolic dysfunction.[12−14] It has been reported that patients with LV with late gadolinium enhancement, which reflects myocardial fibrosis, tend to have recurrent AF and poor improvement in cardiac function.[15,16] One possible explanation is that many factors that influence cardiac function (ischemia, metabolic syndrome, and so on) were observed in the high-risk cohort, so improvement was poor. There is also a report that left ventricular fibrosis is more advanced in patients with PerAF than in those with PAF.[17,18] There appears to be a greater improvement in contractile reserve in group 1 than in group 3, and therefore, this result also supports our previous explanations. The reason why the CHA_2DS_2-VAS_C score has a greater impact on contractile reserve than the type of AF is debatable. One speculation is that the effect of AF itself remained immediately after RFCA but had disappeared by FU-2. Patients with a high CHA_2DS_2-VAS_C score had multiple risk factors without AF that remained at FU-2. In other words, the CHA_2DS_2-VAS_C score might have had a greater impact on the final outcomes. Recently, an improvement in prognosis was reported after ablation in patients with heart failure with reduced ejection fraction and patients with heart failure with preserved ejection fraction.[19−21]

Almost half of our cohort had PerAF, so those patients underwent echocardiography during the AF rhythm. Therefore, the preablation data may have been affected by irregular R-R intervals and tachycardia. Approximately half of the patients in our cohort were expected to have PerAF, and therefore, we designed the protocol to perform preload stress echocardiography only after RFCA to exclude the effect of the AF rhythm in our analyses. The lack of a preload test before RFCA was a limitation in this study. Another limitation of the study was that 20% of patients did not receive the 6-month follow-up test, and therefore, there was a lack of data in these patients. If patients with a reduced LVEF had been included in the study, we might have observed differences in ejection fraction and contractile reserve. Preload stress echocardiography lacks a widely accepted reference range in the literature compared with other well established echocardiographic parameters. Further study is therefore needed to confirm the widely acceptable reference values for this technique.

In conclusion, we showed the detailed changes in LA and LV function after RFCA using preload stress echocardiography. Contractile reserve improved, especially in patients with low CHA_2DS_2-VAS_C scores.

Disclosures

The authors have no conflicts of interest to declare.

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