Correlation between the left atrial low-voltage area and the cardiac function improvement after catheter ablation for paroxysmal atrial fibrillation

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Abstract
Background: The impact of the left atrial low-voltage area (LVA) on the cardiac function improvement following ablation for atrial fibrillation (AF) is unclear.
Methods: In 49 patients with paroxysmal AF who underwent ablation, the left ventricular stroke volume index (SVI) was repeatedly measured using an impedance cardiography until 6 months after ablation. We defined the cardiac function improvement as a 20% increase in the SVI. The LVA (the area with the voltage amplitude of <0.5 mV) was assessed before ablation.
Results: The reduced baseline SVI (<33 mL/m²) was observed in 18 (37%) patients. The SVI increased following ablation (from 36 ± 5 to 39 ± 6 mL/m², P < .001). We observed the cardiac function improvement in 14 (29%) patients. The LVA was smaller in patients with the improved cardiac function than in those without (8.3% ± 5.2% vs 14.0% ± 8.5%, P = .026). The multivariate analysis revealed that only the LVA was independently associated with the cardiac function improvement (odds ratio, 0.878; 95% confidence interval: 0.778-0.991, P = .036). Furthermore, LVAs of the anterior (7.9% ± 7.6% vs 18.2% ± 15.5%, P = .022), septal (12.0 ± 7.3% vs 20.7% ± 13.8%, P = .031), and roof walls (6.9% ± 6.0% vs 16.9% ± 15.2%, P = .022) were smaller in patients with the improved cardiac function than in those without.
Conclusions: The LVA was related to the cardiac function improvement following ablation in patients with paroxysmal AF.

Keywords
atrial fibrillation, cardiac function, catheter ablation, low-voltage area, voltage mapping
1 | INTRODUCTION

Atrial remodeling implies alterations in the morphology and function of the atrium caused by atrial fibrillation (AF) and concomitant diseased conditions. Atrial fibrosis is a hallmark feature of atrial remodeling, resulting in conduction heterogeneity, which facilitates reentry and AF occurrence.\(^1\) In addition, atrial fibrosis is related to atrial contractile dysfunction because it primarily occurs as a reparative process to replace the degenerating myocardial parenchyma with concomitant reactive fibrosis.\(^2,3\)

Some studies\(^4-6\) have reported that catheter ablation for AF improved the cardiac function. However, parameters associated with the cardiac function improvement remain unclear. Since atrial fibrosis correlates with endocardial electrogram amplitudes recorded using bipolar electrodes,\(^7\) the extent of the low-voltage area (LVA) provides a surrogate parameter for the extent of atrial fibrosis. Moreover, previous studies have established a correlation between the left atrial LVA and the left atrial function.\(^8,9\) Hence, the size and location of the LVA could provide some critical information in estimating the cardiac function improvement following AF ablation.

As the cardiac function has been assessed on the basis of the left ventricular ejection fraction previously,\(^4-6\) the recovery of the atrial contractile function might have been undercounted. On the other hand, the stroke volume is a hemodynamic parameter characterizing the global cardiac function, including both atrial and ventricular functions. However, the stroke volume is not frequently used for following up cardiac function because precise measurement of it has usually been performed invasively.

Impedance cardiography (ICG) is a noninvasive method for evaluating the stroke volume based on the measurement of the thoracic bioimpedance.\(^10-13\) We previously revealed the validity of the stroke volume measured using ICG in patients with AF.\(^10\) Being a noninvasive method, ICG can be performed repeatedly. Hence, this study aims to assess the impact of the left atrial LVA on changes in the stroke volume following AF ablation.

2 | METHODS

2.1 | Study population

In this study, we enrolled patients with paroxysmal AF who underwent AF ablation and the voltage mapping at the Toyama University Hospital (Toyama, Japan) between May 2015 and March 2017. We defined paroxysmal AF as AF lasting <7 days. We excluded patients with previous catheter ablation, prior heart surgery, hemodialysis, thyroid diseases, and pulmonary diseases. In addition, if AF recurred during the follow-up period, we excluded patients from the study. Overall, we enrolled 52 patients in this study; however, three patients were excluded because of AF recurrence. Consequently, we assessed 49 patients in this study. We obtained clinical characteristics from medical records. This study protocol was approved by the Institutional Research and Ethics Committee of the University of Toyama (Toyama, Japan) and adhered to the principles of the Declaration of Helsinki. Furthermore, we obtained written informed consent from patients before performing AF ablation.

2.2 | Hemodynamic parameters

We evaluated the stroke volume using ICG (Aesculon® mini; OSYPKA Medical, Berlin, Germany) immediately before ablation, following the day after ablation, and 1, 3, and 6 months after ablation. In all patients, the stroke volume was evaluated during sinus rhythm. All measurements of the stroke volume were performed after taking a resting time of >5 minutes in the supine position until the heart rate and the stroke volume showed a stable value. Briefly, we applied two pairs of surface electrodes located side by side in a vertical direction on the left side of the neck and the left lower thorax at the level of the xiphoid process. Then, we connected the electrodes to an ICG that interpreted the maximum rate of change in the thoracic bioimpedance as the ohmic equivalent of the mean aortic flow acceleration. In addition, the conductivity change because of the change in the blood conductivity was extracted to assess the stroke volume based on the Bernstein-Osypka equation.\(^12\) The stroke volume index (SVI) was evaluated by dividing the stroke volume by the body surface area, which was determined using the DuBois formula.\(^14\) We established a significant correlation between the SVI measured using ICG and that measured using a thermodilution method in our previous study.\(^10\) The SVI measured using ICG tended to be smaller than that measured using thermodilution during sinus rhythm. Notably, we adopted 33-47 mL/m² as a normal range of the SVI.\(^15\) Furthermore, we defined the cardiac function improvement as a 20% increase in the SVI 6 months after ablation and assessed the predictors of the cardiac function improvement after AF ablation.\(^10\)

2.3 | Echocardiography and computed tomography

We performed transthoracic and transesophageal echocardiography before ablation. During transthoracic echocardiography, we measured the left ventricular end-diastolic and end-systolic dimensions from the parasternal long-axis M-mode recordings. Using the Teichholz method, we assessed the left ventricular ejection fraction. Transesophageal echocardiography was performed on patients under sedation using diazepam. Furthermore, we evaluated the left atrial appendage flow velocity during the examination. A reduced left atrial appendage flow velocity was defined as <40 cm/s.

In this study, all patients underwent a contrast-enhanced multi-detector computed tomography within 3 days before ablation. We performed computed tomographic imaging during sinus rhythm in all patients. The left atrial volume was manually evaluated using visualization and analysis software (Synapse Vincent; Fujifilm, Tokyo, Japan). We adopted 21-53 ml as a normal range of the left atrial volume.\(^16\)
2.4 | Catheter ablation

We discontinued all antiarrhythmic drugs for, at least, 5 half-lives, and no patient received oral amiodarone before ablation. Moreover, antiarrhythmic drugs were not resumed after ablation. We used the NavX System (St. Jude Medical Inc., St. Paul, MN) for ablation. The esophageal temperature monitoring system (SensiTherm, St. Jude Medical, Inc.) was used to provide intra-esophageal temperature feedback. Sheath introducers were inserted through the right femoral vein under sedation. We performed the trans-septal procedure and advanced three 8-F SL0 sheaths (St. Jude Medical, Inc.) or two 8-F SL0 sheaths and a steerable sheath (Agilis, St. Jude Medical, Inc.) into the left atrium. After the trans-septal puncture, a single bolus of 5000 U of heparin was administered. A continuous infusion with heparinized saline was performed to maintain an activated clotting time of 300-350 seconds. Pulmonary vein isolation was performed with 3D mapping and guidance using two 7-F decapolar circular catheters (Lasso and Libero), which were positioned at the ipsilateral pulmonary vein ostia. The procedure was completed with cavotricuspid isthmus ablation. Each radiofrequency application was performed for 30-50 s, the temperature was limited to 42°C and power to 30 W. We used the maximum power of 25 W while delivering energy to sites near the esophagus.

2.5 | Voltage mapping

We created the voltage map on the NavX System during sinus rhythm before ablation. In addition, sequential contact mapping of the left atrium was performed using a 7-F decapolar circular catheter (Libero) for the voltage mapping. Contact of the mapping catheter was validated by stable electrograms, the distance to the geometry surface, and concordant catheter motion with the cardiac silhouettes on fluoroscopy. We mapped regions with low-amplitude signals with greater point density to more precisely delineate the LVAs. We assessed the voltage amplitude of each acquired point based on the peak-to-peak bipolar electrogram voltage with a bandpass filter set at 30-300 Hz. The LVAs were delineated on the basis of a bipolar voltage of <0.5 mV. The size of the LVA was shown as a percentage of the LVA to the surface area. For the regional analysis, we divided the left atrium into seven segments, including the anterior wall, septal wall, lateral wall, posterior wall, bottom wall, roof wall, and appendage.

2.6 | Statistical analysis

In this study, data are presented as a mean ± standard deviation with 95% confidence intervals. The significance of between-group differences was analyzed using the unpaired Student’s t test for continuous variables and the chi-squared test for categorical variables. In addition, we analyzed the time-course changes in the hemodynamic parameters using two-way repeated measures analysis of variance. If significant changes were observed, we performed posthoc tests with Bonferroni-adjusted pairwise comparisons. In addition, we performed the univariate and multivariate logistic regression analyses to assess variables associated with the cardiac function improvement. The variables with P < .100 in the univariate analysis were included in the multivariate analysis. Furthermore, receiver-operating characteristic curve analyses were performed to assess the optimal cutoff values for estimating the cardiac function improvement following ablation. We considered P < .050 as statistically significant. Furthermore, statistical analysis was performed using SPSS statistical software for Windows version 16.0 (SPSS Inc., Chicago, IL).

3 | RESULTS

3.1 | Baseline patient characteristics

The mean age of study participants was 65 ± 11 years, and 67% were males (Table 1). The prevalence of congestive heart failure was 6%. Antiarrhythmic drugs, β-blockers, and calcium-channel blockers were administered to 45%, 39%, and 10% of patients, respectively. Although a reduced left atrial appendage flow velocity was observed in three patients, overall, the left atrial appendage

| TABLE 1 Baseline patient characteristics |
|-----------------------------------------|-----------------|-----------------|-----------------|
|                                         | All patients (n = 49) | Improved cardiac function (n = 14) | Nonimproved cardiac function (n = 35) | P value |
| Age, y                                  | 65 ± 11          | 60 ± 10         | 67 ± 10         | .033    |
| Male gender                             | 33 (67)          | 11 (79)         | 22 (63)         | .466    |
| Congestive heart failure                | 3 (6)            | 0 (0)           | 3 (9)           | .628    |
| Hypertension                            | 23 (47)          | 8 (57)          | 15 (43)         | .552    |
| Diabetes mellitus                       | 7 (14)           | 4 (29)          | 3 (9)           | .172    |
| Past history of stroke                  | 5 (10)           | 2 (14)          | 3 (9)           | .932    |
| Antiarrhythmic drugs                    | 22 (45)          | 8 (57)          | 14 (40)         | .436    |
| β-blockers                              | 19 (39)          | 7 (50)          | 12 (34)         | .483    |
| Calcium-channel blockers                | 5 (10)           | 2 (14)          | 3 (9)           | .932    |
| Left atrial appendage flow velocity, cm/s | 71 ± 25         | 75 ± 19         | 70 ± 26         | .566    |
| Left atrial volume, mL                  | 120 ± 31         | 116 ± 17        | 122 ± 35        | .562    |
| Left ventricular end-diastolic dimension, mm | 47 ± 7          | 45 ± 12         | 48 ± 5          | .133    |
| Left ventricular ejection fraction, %   | 65 ± 8           | 63 ± 8          | 65 ± 9          | .368    |
| B-type natriuretic peptide, pg/ml       | 44 ± 57          | 49 ± 53         | 42 ± 60         | .698    |

Note: Data are mean ± SD or number (%) of patients.
flow velocity was preserved. The left atrial dilatation was observed in 48 (98%) patients. The left ventricular end-diastolic dimension and the left ventricular ejection fraction were within the normal range.

3.2 | Time-course changes in hemodynamic parameters

We observed the reduced baseline SVI (<33 mL/m²) in 18 (37%) patients. The prevalence of congestive heart failure and hypertension was more extensive in the reduced baseline SVI group than in the preserved baseline SVI group (congestive heart failure, 20% vs 0%, P = .044; hypertension, 72% vs 32%, P = .009); however, the other parameters were not different between the groups.

The SVI did not change immediately after ablation (from 36 ± 5 mL/m² to 35 ± 6 mL/m²; P = .255; Figure 1A); however, it gradually increased following ablation, and the degree of change attained the statistical significance 1 month after ablation (1 month: 38 ± 6 mL/m², P = .017 vs before ablation; 3 months: 38 ± 5 mL/m², P = .003; 6 months: 39 ± 6 mL/m², P < .001). In addition, the heart rate increased immediately after ablation and remained unchanged after that (Figure 1B). Consequently, the heart rate after 6 months of ablation was higher than that before ablation. Besides the increase in the SVI and heart rate, the cardiac index gradually increased following ablation (Figure 1C).

We observed the cardiac function improvement in 14 (29%) patients. The improved cardiac function group was younger than the nonimproved cardiac function group (Table 1); however, the other parameters were not different between the groups.

3.3 | LVA and the cardiac function improvement

The mean number of mapping points was 729 ± 392. The mean surface area of the left atrium was 86 ± 24 cm², and the mean LVA was 12% ± 8%. The LVA was not different between the reduced baseline SVI group and the preserved baseline SVI group (12.6% ± 8.9% vs 12.2% ± 7.7%, P = .855). In the improved cardiac function group, the LVA was smaller compared with the nonimproved cardiac function group (8.3% ± 5.2% vs 14.0% ± 8.5%, P = .026; Figure 2A). According to the univariate logistic regression analysis, the age and the LVA were applicable to the multivariate analysis (Table 2). We did not include congestive heart failure in the logistic regression analysis because no patient had congestive heart failure in the improved cardiac function group. The multivariate analysis revealed that only the LVA was independently associated with the cardiac function improvement (odds ratio, 0.878; 95% confidence interval: 0.778-0.991, P = .036).

In the regional analysis, the LVAs of each area were as follows: 15.3% ± 14.4% (anterior wall); 18.3% ± 12.8% (septal wall); 11.8% ± 11.6% (lateral wall); 10.5% ± 9.7% (posterior wall); 10.1% ± 8.5% (bottom wall); 14.1% ± 14.0% (roof wall), and 5.8% ± 9.1% (appendage). In addition, LVAs measured at the anterior, septal, and roof walls were smaller in the improved cardiac function group compared with the nonimproved cardiac function group (anterior wall: 7.9% ± 7.6% vs 18.2% ± 15.5%, P = .022; septal wall: 12.0% ± 7.3% vs 20.7% ± 13.8%, P = .031; roof wall: 6.9% ± 6.0% vs 16.9% ± 15.2%, P = .022; Figure 2B). The LVA attained an area under the curve of 0.657 for the ability to estimate the cardiac function improvement; the sensitivity and specificity were 60% and 63%, respectively, for a cutoff value of 9.3%. Figure 3 shows the representative cases of the improved and nonimproved cardiac function groups.

3.4 | Correlation between LVAs and left atrial parameters

In this study, the LVA did not significantly correlate with the left atrial appendage flow velocity (R = −.256, P = .076; Figure 4A). However,
the LVA significantly correlated with the left atrial volume (R = .422, P = .005; Figure 4B).

4 | DISCUSSION

This study assessed the impact of the left atrial LVA on the time-course changes in the SVI following AF ablation in patients with paroxysmal AF. Consequently, we observed a gradual improvement in the cardiac function following ablation, and the small LVA correlated with the cardiac function improvement. In addition, LVAs measured at the anterior, septal, and roof walls primarily correlated with the cardiac function improvement. Furthermore, although a considerable correlation was not observed between the LVA and the left atrial appendage flow velocity, the LVA markedly correlated with the left atrial volume.

4.1 | Impact of the LVAs on the cardiac function improvement

This is the first study to establish a correlation between the left atrial LVA and the cardiac function improvement following ablation. The findings of this study corroborate previous studies, which reported the negative impact of the LVA on the left atrial function. Reportedly, the left atrial LVA correlated with the velocity-time integral of transmural A wave and the left atrial ejection fraction. Furthermore, a speckle-tracking echocardiographic study revealed that the LVA affected the left atrial emptying fraction and left atrial strain.

In patients with the large LVA, the advanced atrial fibrosis might have hindered the recovery of the atrial contractile function following ablation. Some experimental studies have reported that atrial fibrosis is irreversible despite maintaining sinus rhythm. The
strong correlation between LVAs and atrial fibrosis identified by delayed-enhancement magnetic resonance imaging suggests the existence of massive atrial fibrosis in patients with a large LVA. In addition, the LVA might have been a surrogate parameter, which indicated a cardiac overload. As the high left atrial pressure is closely associated with the low left atrial voltage, patients with a large LVA might have had a concurrent diseased condition, which elevated the left atrial pressure. In this study, although only 6% of patients had a history of congestive heart failure, and the mean left ventricular ejection fraction was within the normal range, the baseline SVI was reduced in 37% of patients. These findings suggest the existence of potential cardiac dysfunction, such as diastolic dysfunction, which might have impeded the cardiac function improvement.

In the regional analysis, LVAs of the anterior, septal, and roof walls primarily associated with the cardiac function improvement. Notably, regional differences exist in the left atrial segmental function during atrial contraction, with the posterior wall having the lowest motion, probably because its motion is limited by the attachment of the pulmonary veins or compression by the vertebra. In the literature, the areas of the highest motion are controversial; however, this study corroborates a previous study with cardiac magnetic resonance imaging, which observed high mechanical function in the anterior and septal walls. Hence, the myocardial damage, which was indicated by the LVA, of the anterior, septal, and roof walls might have hindered the recovery of the left atrial function following ablation.

4.2 | Correlation between the LVA and the left atrial parameters

Although the left atrial appendage flow velocity is commonly used as an indicator of the left atrial function, the left atrial appendage flow velocity did not markedly correlate with the LVA in this study. As the LVA of the left atrial appendage was relatively small compared with other areas of the left atrium, the left atrial appendage flow velocity might have not adequately reflected the impairment of the global left atrial function. Conversely, the left atrial volume markedly correlated with LVAs; this finding is consistent with the fact that the higher content of atrial fibrosis is observed in patients with large atria.

4.3 | Clinical implication

LVAs estimated the cardiac function improvement despite the fact that other left atrial parameters, such as the left atrial appendage...
flow velocity and the left atrial volume, were not associated with the cardiac function improvement. LVAs may be a more sensitive marker of atria remodeling than other left atrial parameters. Although the voltage mapping is invasive, it could be crucial to assess the reversibility of atrial remodeling appropriately. Recently, a voltage-guided substrate modification by targeting LVAs has been proposed. In addition, some studies have reported the effectiveness of this additional ablation approach; however, radiofrequency application to the anterior, septal, and roof walls should be avoided to prevent the impairment of the left atrial function.

4.4 | Limitations

This study has some limitations. First, this is a single-center study with a small sample size. Second, we used a decapolar circular catheter (Libero) for the voltage mapping; however, more detailed recordings of local electrograms are possible by using a dedicated mapping catheter with a short interelectrode distance. Third, the validity of the measurement of hemodynamic parameters using ICG measurements has not been established. However, the SVI measured using ICG significantly correlated with that measured using thermodilution during both sinus rhythm and AF rhythm in our previous study. Finally, as we did not directly assess the left atrial function, it remains unclear whether the cardiac function improvement was primarily contributed by the recovery of the left atrial function or the left ventricular function. Hence, further studies that investigate the correlation between LVAs and the improvement in the left atrial function are warranted to draw a definite conclusion.

5 | CONCLUSION

This study reveals that the size and location of the left atrial LVA correlate with the cardiac function improvement following ablation in patients with paroxysmal AF.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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