Left atrial posterior wall isolation affects complex fractionated atrial electrograms in persistent atrial fibrillation

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Abstract
Background: The impact of left atrial posterior wall isolation (LAPWI) on the complex fractionated atrial electrogram (CFAE) is unknown.

Methods: CFAE mapping was performed before and after LAPWI in 46 patients with persistent atrial fibrillation (AF).

Results: LAPWI decreased both the variable (fractionated index ≤ 120 ms; from 60 ± 4 cm² to 50 ± 4 cm², \( P < 0.001 \)) and continuous (fractionated index ≤ 50 ms; from 4.2 ± 1.0 cm² to 3.5 ± 0.9 cm², \( P = 0.036 \)) CFAE areas. Especially, the CFAE areas on the bottom and roof walls of the left atrium and on the posterior and bottom walls of the right atrium significantly decreased after LAPWI. The distribution of variable CFAE areas was not different between the AF-recurrence (\( n = 9 \)) and AF-free (\( n = 37 \)) groups before LAPWI; however, it was larger in the anterior and septal walls of the right atrium in the AF-recurrence group than in the AF-free group after LAPWI (anterior wall, 8% ± 2% vs 5% ± 1%, \( P = 0.048 \); septal wall, 23% ± 4% vs 16% ± 1%, \( P = 0.043 \)). The distribution of continuous CFAE areas on the bottom wall of the right atrium was larger in the AF-recurrence group than in the AF-free group both before LAPWI (30% ± 20% vs 4% ± 2%, \( P = 0.008 \)) and after LAPWI (25% ± 25% vs 3% ± 1%, \( P = 0.027 \)).

Conclusions: LAPWI decreased the CFAE areas and affected their distribution, which contributed to AF recurrence.

KEYWORDS
atrial fibrillation, catheter ablation, complex fractionated atrial electrogram, left atrial posterior wall isolation, pulmonary vein isolation

1 INTRODUCTION

Since the initial report that majority of the triggers for atrial fibrillation (AF) reside within the pulmonary veins,1 pulmonary vein isolation has become the cornerstone technique of catheter ablation for paroxysmal AF. However, pulmonary vein isolation alone was found to be less effective for persistent AF than for paroxysmal AF, because the mechanisms of the former include complex atrial substrates and non-pulmonary vein triggers.2–4 Although some additional ablation approaches, such as the electrogram-based ablation...
and linear ablation, have been proposed, the outcomes of catheter ablation for persistent AF remain unsatisfactory.\(^5\)

The left atrial posterior wall embryologically originates from the same cells of the primordial pulmonary vein.\(^6\) Moreover, the myocytes of the left atrial posterior wall have a relatively high incidence of delayed after-depolarizations because of their distinctive ion channel characteristics.\(^7\) Consequently, focal discharges from the left atrial posterior wall play an important role as the non-pulmonary vein trigger for the initiation of AF.\(^8\) Additionally, the complex structure of the left atrial posterior wall with the abrupt change in muscle fiber orientation contributes to the frequent finding of AF drivers and rotors.\(^9\),\(^10\)

Left atrial posterior wall isolation (LAPWI) has been part of the surgical Maze procedure and has yielded good results as an open surgical procedure.\(^11\) Although LAPWI is challenging to achieve with the use of endocardial catheter ablation,\(^12\),\(^13\) some previous studies have reported the effectiveness of LAPWI to suppress AF recurrence after catheter ablation.\(^14\)–\(^17\) However, the mechanisms of the AF-suppressing effects of LAPWI are still unclear.

Complex fractionated atrial electrogram (CFAE), which demonstrates continuous fractionation and very short cycle lengths during AF, provides valuable information regarding the substrate of AF.\(^18\) Therefore, assessment of changes in the CFAE areas after LAPWI may be useful for understanding the mechanisms of the AF-suppressing effects of LAPWI. Especially, changes in the CFAE areas in the right atrium, which is remote from the LAPWI lines, may provide new insights into the mechanisms of the AF-suppressing effects of LAPWI. Therefore, the aim of the present study was to assess the impact of LAPWI on the size and distribution of CFAE areas in persistent AF patients. In addition, the relationship between the CFAE areas and AF recurrence after catheter ablation was assessed.

2 | METHODS

2.1 | Study population

The subjects enrolled in the present study comprised 46 patients with persistent AF who underwent AF ablation at the Toyama University Hospital from November 2015 to October 2016. Persistent AF was defined as AF lasting ≥ 7 days.\(^19\) Patients with previous catheter ablation or previous heart surgery, those on he- modialysis, and those with thyroid and pulmonary diseases were excluded. The study protocol was approved by the Institution Research and Ethics Committee of the University of Toyama and was conducted in accordance with the principles of the Declaration of Helsinki. We obtained written informed consent from the patients before performing catheter ablation.

2.2 | AF Ablation and CFAE mapping

All antiarrhythmic drugs were discontinued for at least five half-lives, and no patient received oral amiodarone before the ablation. Sheath introducers were inserted through the right femoral vein, with the patient under sedation. A transseptal procedure was performed; two 8-F SL0 sheaths and a steerable sheath (Agilis, St. Jude Medical, Inc.) were advanced into the left atrium. A three-dimensional (3D) atrial geometry was created on the NavX system (St. Jude Medical Inc., St. Paul, MN, USA) using 7-F decapolar circular catheters (Lasso, Biosense-Webster, Inc., Diamond Bar, CA, USA; Libero, Japan Lifeline Co., Ltd., Tokyo, Japan).

Pulmonary vein isolation was performed with guidance using two 7-F decapolar circular catheters (Lasso and Libero) that were positioned at the ipsilateral pulmonary vein ostia. The first CFAE mapping was performed following pulmonary vein isolation. A left atrial roof line at the most cranial aspect and a floor line joining the most inferior margin of the pulmonary vein isolation line were created for LAPWI. The entrance block was confirmed by voltage mapping using a 3D mapping system. The second CFAE mapping was performed following LAPWI. The exit block was confirmed using high-output pacing within the LAPWI lines after external cardioversion. The procedure was completed after creating a block line on the mitral isthmus and on the cavotricuspid isthmus. Each radiofrequency application was performed for 30-50 seconds. The temperature was maintained at 42°C and power at 30 W; a maximum power of 25 W was used while delivering energy to the sites near the esophagus.

Sequential contact mapping was performed using a 7-F decapolar circular catheter (Libero). Contact of the mapping catheter was confirmed by stable electrograms, the distance to the geometry surface, concordant catheter motion with the cardiac silhouettes on fluoroscopy. For CFAE mapping, fractionation analyses were performed on the NavX system. The mapping parameter was defined as an interval analysis algorithm that evaluated the average index of the fractionation. The settings of CFAE mapping were peak-to-peak sensitivity of 0.04 mV, electrogram refractory period of 30 ms, electrogram width of < 10 ms, and electrogram segment length of 5 seconds. The fractionated index was defined as the average time interval between consecutive deflections during a duration of the recording. A previous study\(^20\) reported that transiently fractionated electrograms were observed at the areas with a fractionated index of 50-120 ms (variable CFAE areas), and continuously fractionated electrograms were seen at the areas with a fractionated index of ≤ 50 ms (continuous CFAE areas). Both the variable and continuous CFAE areas may play a role in the maintenance of AF; however, the continuous CFAE areas may be more crucial than the variable CFAE areas. Therefore, we assessed the size and distribution of the variable and continuous CFAE areas separately. Analyses of the CFAEs were performed in 605 ± 49 points. For the regional analysis of the CFAE areas, the left atrium was divided into seven segments, including the anterior wall, septal wall, lateral wall, posterior wall, bottom wall, roof wall, and appendage. The right atrium was divided into five segments, including the anterior wall, septal wall, lateral wall, posterior wall, and bottom wall.

2.3 | Post-procedure care and follow-up

We conducted clinical interview and performed surface electrocardiogram on the day following the ablation and during monthly visits to the outpatient clinic thereafter. In addition, we performed...
24-hour Holter monitoring on the day following ablation and as needed thereafter the follow-up period. Antiarrhythmic drugs were discontinued at the discretion of the treating physician. The follow-up was performed until 12 months after ablation. AF recurrence was defined as sustained AF lasting > 30 seconds, which occurred from 3 to 12 months after catheter ablation.

2.4 | Statistical analyses

The data were presented as mean ± standard error of the mean. The significance of the changes in the CFAE areas was analyzed using paired Student’s t test. Patients were divided into two groups according to the presence of AF recurrence after catheter ablation. The distribution of the CFAE areas was compared between the groups to assess the impact of the location of the CFAE areas on AF recurrence. The distribution of CFAE areas was defined as the proportion of CFAE areas in each segment of the atria relative to the cumulative CFAE areas. The significance of the differences between the groups was analyzed using unpaired Student’s t-test for continuous variables and Fisher’s exact probability test for categorical variables. The correlations between the surface area of LAPWI and changes in the CFAE areas were analyzed using the Pearson’s correlation coefficient. A P < 0.05 was accepted as statistically significant.

3 | RESULTS

3.1 | Patient characteristics and outcomes after catheter ablation

The baseline patient characteristics are shown in Table 1. The mean AF duration was over 1 year. Over half of the patients had hypertension, and 20% had congestive heart failure. Left atrial appendage flow velocity deteriorated, but left atrial dilatation was mild.

| Note. Data are mean ± SE or number (%) of patients. Abbreviation: AF, atrial fibrillation.

| TABLE 1 Baseline patient characteristics |
|------------------------------------------|
| **All patients** | **AF-recurrence group** | **AF-free group** | **P value** |
| Age, years (n = 46) | 64 ± 1 | 67 ± 3 | 63 ± 2 | 0.258 |
| Male gender | 39 (85) | 6 (67) | 33 (89) | 0.242 |
| AF duration, months | 16 ± 3 | 10 ± 3 | 17 ± 4 | 0.341 |
| Congestive heart failure | 9 (20) | 3 (33) | 6 (16) | 0.489 |
| Hypertension | 24 (52) | 4 (44) | 20 (54) | 0.884 |
| Diabetes mellitus | 4 (9) | 0 (0) | 4 (11) | 0.709 |
| Past history of stroke | 6 (13) | 0 (0) | 6 (16) | 0.457 |
| Antiarrhythmic drug before ablation | 5 (11) | 0 (0) | 5 (14) | 0.568 |
| Antiarrhythmic drug after ablation | 22 (48) | 5 (56) | 17 (46) | 0.884 |
| Left atrial appendage flow velocity, cm/s | 37 ± 3 | 42 ± 9 | 36 ± 3 | 0.465 |
| Left atrial dimension, mm | 43 ± 1 | 45 ± 1 | 43 ± 1 | 0.458 |

Complex fractionated atrial electrogram mapping was completed in all patients because there was no spontaneous termination of the AF during the procedure. LAPWI was successfully performed in all patients. Ectopic activity originating inside LAPWI was observed in only one patient. After catheter ablation, AF recurred in nine patients (20%). Three patients underwent a second catheter ablation procedure; in one of the patients, reconnection of the LAPWI was observed, and LAPWI was achieved during radiofrequency application on the floor line. The baseline patient characteristics were not different between the AF-recurrence and the AF-free groups (Table 1).

3.2 | Changes in the CFAE areas after LAPWI

A representative case of the changes in the CFAE areas after LAPWI is shown in Figure 1. The variable CFAE areas significantly decreased after LAPWI in both the left and right atria (Figure 2A,B). Therefore, the total variable CFAE area decreased after LAPWI (Figure 2C). The continuous CFAE areas did not change after LAPWI in the left atrium (Figure 2D), but they significantly decreased in right atrium (Figure 2E). Consequently, the total continuous CFAE areas significantly decreased after LAPWI (Figure 2F).

The mean surface area of LAPWI was $11 \pm 1 \text{ cm}^2$. Significant correlations between the surface area of LAPWI and changes in the variable ($R = 0.017, P = 0.912$) or continuous ($R = 0.030, P = 0.843$) CFAE areas were not observed.

3.3 | Changes in the regional CFAE areas after LAPWI

Both the variable and continuous CFAE areas were exclusively distributed on the anterior and septal walls of the left atrium and on the septal and lateral walls of the right atrium before LAPWI (Figure 3A,B). After LAPWI, the variable CFAE areas significantly decreased on the posterior, bottom, and roof walls of the left atrium.
and on the posterior and bottom walls of the right atrium (Figure 3A). The continuous CFAE areas significantly decreased on the posterior and bottom walls of the right atrium (Figure 3B).

3.4 | Comparison of the CFAE areas according to the recurrence of atrial fibrillation

The distribution of the variable CFAE areas did not differ between the groups before LAPWI (Figure 4A), but that on the anterior and septal walls of the right atrium became significantly larger in the AF-recurrence group than in the AF-free group after LAPWI (Figure 4B). The distribution of the continuous CFAE areas on the bottom wall of the right atrium was larger in the AF-recurrence group than in the AF-free group before LAPWI (Figure 5A), and this difference was maintained after LAPWI (Figure 5B).

4 | DISCUSSION

In this study that assessed the impact of LAPWI on the CFAE areas, we found that LAPWI significantly decreased both the variable and continuous CFAE areas, not only in the posterior wall of the left atrium but also in the other segments of both the left and right atria. In particular, the CFAE areas on the bottom and roof walls of the left atrium and on the posterior and bottom walls of the right atrium significantly decreased. After LAPWI, a large distribution of the CFAE areas in the right atrium was associated with AF recurrence after catheter ablation.

4.1 | Mechanisms of decrease in the CFAE areas after LAPWI

The reduction of atrial myocardial mass may explain the decrease in the CFAE areas after LAPWI.21,22 LAPWI may have decreased AF drivers...
by debulking an atrial myocardial mass and consequently decrease the CFAE areas. Furthermore, the CFAE areas in the roof and bottom walls of the left atrium were especially decreased after LAPWI. Meandering of the AF rotors contributes to the formation of fractionated potentials. Therefore, the decreases in the CFAE areas on the roof and bottom walls of the left atrium, which are close to the LAPWI lines, suggested that the meandering of the AF rotors was hindered by the LAPWI lines. In addition, the CFAE areas in the anterior and septal walls of the left atrium did not decrease after LAPWI, although the total CFAE areas decreased after LAPWI. This finding suggested that the meandering center of the AF rotors may have shifted from the roof and bottom walls to the anterior and septal walls of the left atrium. A previous study reported a high AF freedom rate by adding LAPWI and the anterior line to pulmonary vein isolation. This additional anterior line may have eliminated the AF rotors that were shifted to the anterior wall after LAPWI.

Furthermore, parasympathetic denervation may have contributed to a decrease in CFAE areas. Since parasympathetic fibers and muscarinic receptors are preferentially located in the posterior wall of the left atrium, LAPWI attenuates parasympathetic nerve activities and increases sympathovagal balance. Parasympathetic activity causes the release of acetylcholine, which acts predominantly on M2 receptors to activate the G-protein-activated potassium current (I_{KAC}) and shorten the duration of the action potential and effective refractory period. Therefore, parasympathetic denervation may have caused prolongation of the effective refractory period of the atria, resulting in the prolongation of AF cycle length. The regional differences in the degree of changes in the CFAE areas throughout the atria may have been partly related to the heterogeneity in the distribution of I_{KAC}.

4.2 Impacts of the CFAE areas on AF recurrence

In the AF-recurrence group, the distribution of the variable CFAE areas shifted from the left atrium to the right atrium after LAPWI. In
addition, the continuous CFAE areas on the bottom wall of the right atrium were larger in the AF-recurrence group than in the AF-free group. These findings suggested that the remaining CFAE areas in the right atrium after LAPWI were associated with AF recurrence after catheter ablation. Although the determinants of the shift of the CFAE areas to the right atrium were not assessed in the present study, myocardial damage in the right atrium was probably associated with AF recurrence after LAPWI. Moreover, although we created a cavotricuspid isthmus line, the continuous CFAE areas on the bottom wall of the right atrium were still associated with AF recurrence. Since we did not perform radiofrequency application according to the continuous CFAE areas, these areas may not have been sufficiently ablated.

4.3 | Clinical implication

Left atrial posterior wall isolation may unmask the potential AF substrates in the right atrium because the differences in the various CFAE areas appeared after LAPWI. In patients with large CFAE areas in the right atrium after LAPWI, suppression of AF recurrence is insufficient with LAPWI alone. A previous study reported that radiofrequency application to the CFAE areas, in addition to LAPWI and the anterior line, did not increase the AF freedom rate; however, the right atrial CFAE areas were not assessed in that study. Therefore, the additional radiofrequency application targeting the right atrial CFAE areas might improve outcome. However, further studies are needed because a few studies revealed the effectiveness of radiofrequency application targeting the right atrial CFAE areas.

4.4 | Limitations

Our study should be interpreted in the context of the following limitations. First, the number of patients included was too small to draw definite conclusions. Second, although the CFAEs are considered to represent the rapid electrical activity from the AF drivers, some may be a result of the dyssynchronous activation of separate cell groups at pivot points, wave collisions, or far-field potentials. Therefore, the CFAE areas do not necessarily represent the AF drivers. Nevertheless, the CFAE areas should provide crucial information on the AF substrate. Third, although low-voltage areas are known to be associated with atrial remodeling, their influence on the CFAE areas was not assessed in this study. Low-voltage areas should be assessed during sinus rhythm; however, if cardioversion was performed before catheter ablation, AF might not have been induced and the CFAE areas could not be assessed. Fourth, LAPWI may have suppressed AF recurrence by eliminating AF trigger from the posterior wall of the left atrium; however, we observed the ectopic activity originating inside LAPWI in only one patient after ablation. Lastly, the contribution of LAPWI reconnection on AF recurrence was not completely excluded because only three of nine patients with AF recurrence received a second procedure. However, LAPWI reconnection was not observed in almost all patients who received a second procedure.

5 | CONCLUSION

Left atrial posterior wall isolation decreased the CFAE areas and changed the distribution of the CFAE areas. The remaining CFAE areas in the right atrium after LAPWI were associated with AF recurrence after catheter ablation.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.
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