

**Original****Large Right Pulmonary Vein Is a Predictor of Atrial Fibrillation Recurrence after Pulmonary Vein Isolation in Patients with Persistent Atrial Fibrillation**

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**Abstract** : Pulmonary vein isolation (PVI) is an effective treatment for atrial fibrillation (AF). However, outcomes differ between paroxysmal AF and persistent AF. We analyzed the predictors of recurrence by examining the recurrence group after ablation. Of 372 consecutive patients with AF who underwent PVI between June 2016 and December 2018, we evaluated 250 patients (age,  $67 \pm 12$  y, 65% men) whose left atrium (LA) was constructed using the PENTARAY catheter (BioSense Webster, Los Angeles, CA), a multipolar electrode catheter with a novel shape and excellent mapping capability. We measured the LA total volume (LATV), right pulmonary vein + antrum volume (RPAV), left PV + antrum volume (LPAV), LA central volume (LACV), and LA bipolar voltage. Of the 250 patients, 78 had persistent AF (recurrence, 20) and 172 had paroxysmal AF (recurrence, 16). In all patients, LATV, LACV, RPAV, and LPAV were significantly larger in patients with persistent AF than those with paroxysmal AF. The mean LA bipolar voltage in patients with persistent AF was significantly lower than those with paroxysmal AF. In cases of persistent AF, RPAV was significantly larger in the recurrence group than that in the non-recurrence group ( $15.9 \pm 4.8$  vs  $13.4 \pm 5.4$  ml;  $P < 0.05$ ). In cases of paroxysmal AF, there were no differences in any volume between the recurrence and non-recurrence groups. In conclusion, larger right PV is a predictor of AF recurrence after PVI in patients with persistent AF. The right PV is close to the atrial septum and the septopulmonary bundle, and the expansion of RPAV reflects the disruption of these structures, which may be involved in this result.

**Key words** : atrial fibrillation, electroanatomical mapping, left atrial volume, pulmonary vein isolation, septopulmonary bundle

**Introduction**

Catheter-based pulmonary vein (PV) ablation is a successful treatment for symptomatic atrial

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fibrillation (AF)<sup>1,2</sup>. Electrical pulmonary vein isolation (PVI) is an essential endpoint for successful outcome<sup>2-4</sup>. However, there is a significant difference in the rate of recurrence after PVI between paroxysmal AF and persistent AF. It is suggested that the difference in treatment outcomes may reflect the fact that these are different diseases. Previous reports have evaluated the anatomical characteristics of paroxysmal and persistent AF using echocardiography, contrast computed tomography CT, and cardiac magnetic resonance imaging<sup>5-7</sup>. In the present study, we simultaneously evaluated the anatomical and electrical characteristics of paroxysmal and persistent AF using high-density 3-dimensional electroanatomical mapping and the PENTARAY catheter (BioSense Webster, Los Angeles, CA), a multipolar electrode catheter with a novel shape and excellent mapping capability. The objective of this study was to determine whether there were any differences in left atrium (LA) and PV volume measured by the PENTARAY catheter in paroxysmal and persistent AF. We also determined the predictors of recurrence by analyzing the recurrence groups after ablation.

## **Patients and methods**

### *Study design*

This was a single-center, retrospective observational study. The study participants were 372 consecutive symptomatic patients undergoing AF ablation at Showa University Koto Toyosu Hospital between June 25, 2016 and December 13, 2018. AF type was categorized as paroxysmal (lasting < 1 wk) or persistent (lasting > 1 wk). These categories were adopted from the guidelines of the Japanese Circulation Society<sup>8,9</sup>.

### *Procedures*

We used the BioSense Webster CARTO3 V6 (BioSense Webster) 3-dimensional mapping system in all cases. Mapping and ablation were performed using the PENTARAY catheter, SOUNDSTAR catheter (BioSense Webster), and VisiTag module (BioSense Webster).

CARTO3 is the third-generation electroanatomical mapping system from Biosense Webster and is currently available with the latest software version 6<sup>10</sup>. The multielectrode mapping catheter was a 20-pole steerable mapping catheter arranged in 5 soft radiating spines covering a diameter of 3.5 cm (PENTARAY; Diamond Bar, interelectrode spacing, 2-6-2 mm; multielectrode mapping)<sup>11</sup>. The PENTARAY catheter can acquire points by stroking the LA surface better than a conventional ring catheter. It is then possible to create a geometry similar to that of the LA, constructed by contrast-enhanced CT. The SOUNDSTAR catheter is an ultrasound catheter specifically for use inside the heart chamber<sup>12</sup>. A magnetic sensor and an ultrasonic probe are mounted at the tip of the catheter<sup>12</sup>. The VisiTag module is the first type of electrophysiology technology to incorporate parameters of lesion formation that can be indexed by the user, according to the ablation strategy<sup>13</sup>. The catheter position stability (minimum time in seconds and maximum range of movement in millimeters), the force-over-time (minimum value in grams and percentage above this value), the impedance drop, and the target temperature can be selected as parameters of lesion formation (so-called filter thresholds) for displaying the radiofre-

quency tag<sup>13</sup>). We divided the LA and PV with reproducibility by using the VisiTag module.

### *LA mapping*

We mapped the LA with the PENTARAY catheter before and after the creation of ablation lines. A 6-Fr 16-pole catheter (BeeAT; Japan-Life-Line Co., Ltd., Tokyo, Japan) was placed in the coronary sinus (CS) through the right jugular vein or left subclavian vein for pacing, recording, and internal cardioversion. LA volume was constructed using fast anatomical mapping, the PENTARAY catheter, and the SOUNDSTAR catheter during CS distal pacing. In patients with persistent AF, electrical defibrillation was performed before ablation to return to sinus rhythm. We then mapped during CS distal pacing. Thus, all patients were measured under the same conditions. Fast anatomical mapping and detailed bipolar voltage maps were created using 2–6–2-mm spacing PENTARAY with a color fill threshold of 5 mm, aiming for complete coverage of the LA and PVs. Intracardiac electrograms were filtered from 16 to 500 Hz and measured at a sweep speed of 100 mm/s. Criteria for including points on the map using the CONFIDENSE continuous mapping module (BioSense Webster) included a cycle length stability within a 5% range of the total cycle length, an electrode position stability within 3 mm, a local activation time stability filter at 5 ms, and tissue proximity to the endocardial surface. Low voltage areas were defined as sites with a bipolar voltage less than 0.1 mV.

### *Measurement of left atrial volume and left atrial bipolar voltage amplitude*

We used LA voltage mapping obtained by the PENTARAY catheter to measure LA volume. The range of LA total volume (LATV) was defined as the area of bilateral PVs where a voltage of more than 0.1 mV was recorded (Fig. 1A). We divided a LATV in 3 volumes using a line in VisiTag of the ablation. We defined the 3 volumes as LA central volume (LACV), right PV + antrum volume (RPAV), and left PV + antrum volume (LPAV) (Fig. 1B). We counted the number of LA mapping points and the mean LA bipolar voltage amplitude collected in the LA mapping using the PENTARAY catheter (Fig. 2).

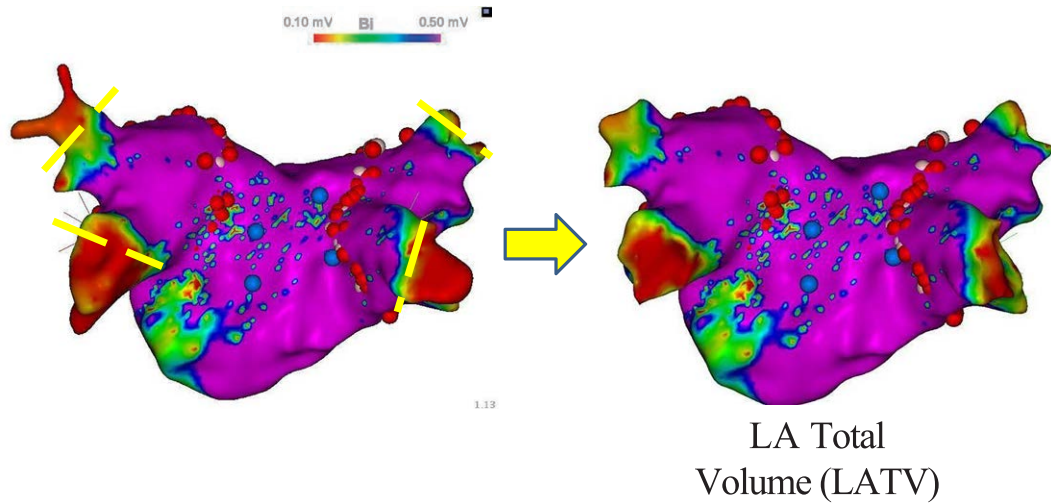
### *Correlation with LA volume obtained using contrast CT*

We performed contrast CT before ablation and evaluated LA volume in the first 15 patients. The mean lengths of the myocardial sleeves of the 4 veins were assumed to be 14 mm for the left superior PV, 12 mm for the right superior PV, 9 mm for the left inferior PV, and 6 mm for the right inferior PV<sup>14</sup>). As shown in Figure 3, we excluded PV volume at each length from PV + LA volume obtained using contrast CT, and defined volume as LA total volume-CT (LATV-CT).

### *Ablation protocol*

All patients underwent PVI. Ablation was performed by 4 electrophysiologists using a 3.5-mm tip irrigated ablation catheter (ThermoCool SmartTouch SF; BioSense Webster). Energy was delivered at 25 to 50 W with a target contact force of 4 to 20 grams. The ablation endpoint

A

**Measurement of LA total volume**

B

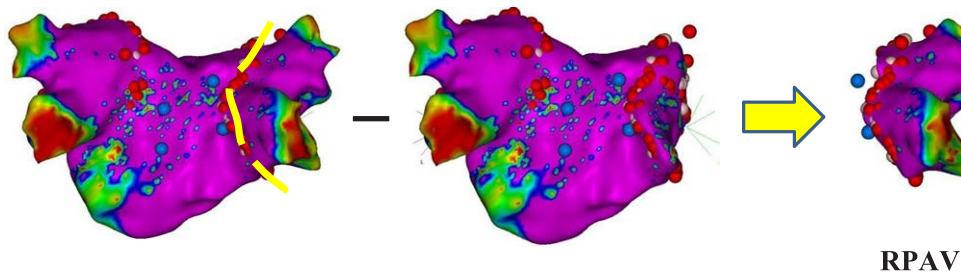
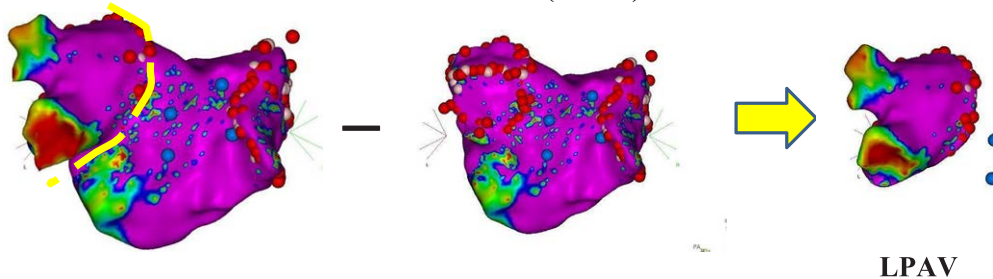
**Measurement of Right PV + antrum volume (RPAV)****Measurement of Left PV + antrum volume (LPAV)**

Fig. 1. A, Measurement of LA total volume (LATV) obtained by LA voltage mapping. The range of LATV was defined as the area of bilateral pulmonary veins where a voltage of more than 0.1 mV was recorded. B, Measurement of the right PV + antrum volume (RPAV) and left PV + antrum volume (LPAV). We divided the LATV in 3 parts using VisiTag.

was confirmation of entrance and exit block at the PVs. The line of ablation was chosen at the atrial side of the PV antrum, depending on the operator's judgment. Complete PVI was achieved in all patients. After discharge, we observed the patients with 0 days as the day of ablation. Electrocardiogram and Holter monitoring were conducted in an outpatient clinic.



Fig. 2. Measurement the number of LA mapping points and the mean LA bipolar voltage amplitude collected in the left atrium mapping using the PENTARAY catheter.

#### Measurement of LATV using contrast CT



Fig. 3. Measurement of LA total volume-CT (LATV-CT). Mean lengths of the myocardial sleeves of the 4 veins were assumed to be 14 mm for the left superior PV, 12 mm for the right superior PV, 9 mm for the left inferior PV, and 6 mm for the right inferior PV. We excluded PV volume at each length from PV + LA volume obtained using contrast CT, and defined volume as LATV-CT.

Patients were asked to contact our study team if they experienced any discomfort. A 3-month postprocedure blanking period was applied. Recurrence was defined as AF detected by ECG or Holter ECG after the 3-month blanking period. In all patients, the follow-up period was completed at 1 year if there was no recurrence.

### Statistical analysis

Statistical analyses were performed using JMP14 (SAS Institute Inc, Cary, NC). Continuous variables are displayed as mean  $\pm$  standard deviation. Categorical variables were presented as number and percentage. The Student *t* test was used for comparison of continuous variables. Categorical variables were reported as count and percentages and were compared using the chi-square test. To evaluate the accuracy of the LA volume measured using the PENTARAY catheter, we plotted and analyzed the LATV obtained by contrast CT and LATV obtained using the PENTARAY catheter. The best-fit curves were determined based on the R-squared statistic. Correlation coefficient analysis was performed using the Pearson product-moment correlation coefficient, depending on the normality of the distribution. A *P* value less than 0.05 was deemed significant.

### Ethics approval

This study plan was approved by the Showa University Clinical Research Review Board (approval number: 19T7043) and conformed to the principles of the Declaration of Helsinki. All patients provided written informed consent.

## Results

### Patient characteristics

Of the 372 patients initially screened, 250 met all the study criteria (Fig. 4). Patient characteristics are shown in Table 1. The mean duration of AF in patients with persistent AF was 20 months (minimum, 3 mo; maximum, 72 mo). Eleven patients had valvular disease, 4 of whom had mitral valve disease (3 cases of mitral regurgitation, 1 case of mitral stenosis) and 7 of whom had aortic regurgitation. The mean observation period was 278 days.

### LA volume measured using the PENTARAY Catheter

The mean LATV in all patients was  $113.3 \pm 32.2$  ml, and the mean LACV was  $90.4 \pm 29.1$  ml. The mean LPAV was  $10.5 \pm 4.6$  ml, and the mean RPAV was  $12.5 \pm 4.5$  ml. There were 833  $\pm$

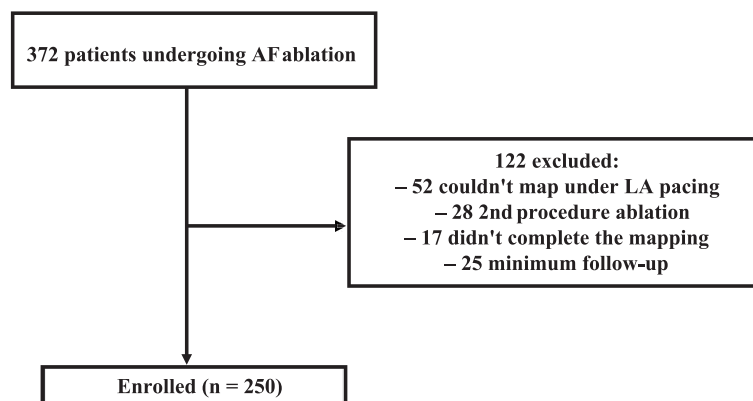


Fig. 4. Flow chart illustrating inclusion and exclusion of the study

Table 1. Clinical, echocardiographic, and electromapping characteristics

	Paroxysmal AF (n = 172)	Persistent AF (n = 78)	<i>P</i> value
Age, y	67 ± 12	67 ± 11	NS
Male, n (%)	99 (58)	64 (82)	< 0.05
Height, cm	162.7 ± 10.6	166.3 ± 9.1	< 0.05
Weight, kg	64.1 ± 13.5	68.8 ± 13.6	< 0.05
Body surface area, m <sup>2</sup>	1.7 ± 0.2	1.8 ± 0.2	< 0.05
Hypertension, n (%)	85 (50)	45 (58)	NS
Dyslipidemia, n (%)	48 (28)	27 (35)	NS
Coronary artery disease, n (%)	14 (8.1)	8 (10)	NS
Diabetes mellitus, n (%)	21 (12)	16 (21)	NS
Heart failure, n (%)	12 ( 7)	17 (22)	< 0.05
Stroke, n (%)	18 (11)	6 ( 8)	NS
Valvular disease, n (%)	6 ( 4)	5 ( 6)	NS
CHADS2 score	1.1 ± 1.1	1.3 ± 1.2	NS
Duration of AF, mo	-	20	
Echocardiography			
Left atrial diameter, mm	39.1 ± 7.0	50.0 ± 46.7	< 0.05
Left atrial volume, ml	57.7 ± 18.3	84.1 ± 26.1	< 0.05
Left atrial volume index, ml/m <sup>2</sup>	34.6 ± 11.3	48.3 ± 15.2	< 0.05
LV ejection fraction, %	64.0 ± 7.7	54.9 ± 11.6	< 0.05
3D-mapping			
Number of LA mapping points	830 ± 405	842 ± 357	NS
LA bipolar voltage amplitude, mV	1.02 ± 0.42	0.69 ± 0.23	< 0.05
LATV, ml	100.9 ± 22.2	140.6 ± 34	< 0.05
LACV, ml	79.9 ± 21.1	113.7 ± 31	< 0.05
RPAV, ml	11.7 ± 3.9	14.1 ± 5.3	< 0.05
LPAV, ml	9.5 ± 3.6	12.8 ± 5.8	< 0.05

Student's *t* test and chi-square test were used for independent samples. *P* value indicates a statistically significant difference at the level of 5%. Values with ± indicate mean and standard deviation.

AF, atrial fibrillation; LA, left atrium; LATV, left atrial total volume; LACV, left atrial central volume; LPAV, left PV + antrum volume; LV, left ventricular; NS, not significant; RPAV, right PV + antrum volume.

394 LA mapping points. The mean LA bipolar voltage amplitude was  $0.96 \pm 0.41$  mV. There was no correlation between LAV measured by echocardiography and LATV. To calculate the correlation between the LA volume evaluated using the PENTARAY catheter and the LA volume measured using contrast CT, we performed contrast CT before ablation and evaluated LA volume in the first 15 patients. The mean LATV-CT was  $119.5 \pm 26.2$  ml. As shown in Figure 5, LATV-PENTARAY significantly correlated with LATV-CT (Fig. 5).

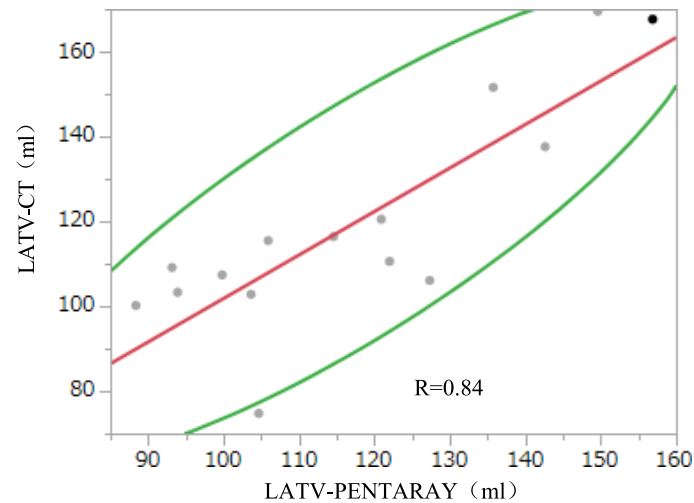


Fig. 5. Correlation diagram between LATV-CT and LATV-PENTARAY. LATV-PENTARAY significantly correlated with LATV-CT.

#### *Paroxysmal AF and persistent AF*

Table 1 shows a comparison between the paroxysmal AF and persistent AF groups. Of the 250 patients, 172 had paroxysmal AF and 78 had persistent AF. In the paroxysmal AF group, 99 patients (58%) were men. In the persistent AF group, 64 patients (82%) were men. In terms of height, weight, and body surface area, the persistent AF group demonstrated significantly larger values than the paroxysmal AF group. The proportion of patients with heart failure was higher in the persistent AF group. The number of LA mapping points between the persistent AF and paroxysmal AF groups were not different. As shown in Table 1, the mean LA bipolar voltage of the persistent AF group was significantly lower than that of the paroxysmal AF group, and each of the 4 volumes (LATV, LACV, RPAV, and LPAV) was significantly larger in the persistent AF group than in the paroxysmal AF group.

#### **Recurrence**

Among all patients, 36 (14.4%) experienced recurrences after PVI. There were 16 patients (9%) with recurrence in the paroxysmal AF group. In patients with PAF, there was no significant difference in number of LA mapping points, average LA bipolar voltage amplitude, or volume between the recurrence and non-recurrence groups (Table 2A). Also, there was no significant difference in the number of LA mapping points, average LA bipolar voltage amplitude, LATV, LACV, or LPAV between the 2 groups in patients with persistent AF. RPAV was the only variable that demonstrated a significant difference between the recurrence and non-recurrence groups (Table 2B).

#### **Discussion**

##### *Main findings*

The main findings of this study were as follows: (1) we measured 4 volumes and LA bipolar



Table 2.

## A. Analysis of recurrence in the paroxysmal AF group

	Nonrecurrence group (n = 156)	Recurrence group (n = 16)	P value
Number of LA mapping points	819 ± 399	928 ± 469	NS
LA bipolar voltage amplitude, mV	1.04 ± 0.42	0.87 ± 0.45	NS
LATV, ml	101.1 ± 22.3	98.3 ± 21.8	NS
LACV, ml	80.1 ± 21	77.4 ± 22.5	NS
RPAV, ml	11.8 ± 3.9	11.2 ± 4.1	NS
LPAV, ml	9.4 ± 3.6	10.2 ± 3.7	NS

LA, left atrium; LATV, left atrial total volume; LACV, left atrial central volume; LPAV, left PV + antrum volume; NS, not significant; RPAV, right PV + antrum volume.

## B. Analysis of recurrence in the persistent AF group

	Non-recurrence group (n = 58)	Recurrence group (n = 20)	P value
Number of LA mapping points	862 ± 394	777 ± 202	NS
LA bipolar voltage amplitude, mV	0.71 ± 0.23	0.63 ± 0.27	NS
LATV, ml	140.1 ± 33.3	142.1 ± 36.9	NS
LACV, ml	113.8 ± 29.9	113.6 ± 34.9	NS
RPAV, ml	13.4 ± 5.4	15.9 ± 4.8	< 0.05
LPAV, ml	12.8 ± 6.2	12.8 ± 4.7	NS

LA, left atrium; LATV, left atrial total volume; LACV, left atrial central volume; LPAV, left PV + antrum volume; NS, not significant; RPAV, right PV + antrum volume.

voltage amplitude using the PENTARAY catheter; (2) persistent AF patients had larger values than paroxysmal AF patients for all volumes measured; (3) the LA of persistent AF patients showed a decrease in the voltage amplitude of the entire LA; (4) there was no association between the 4 volumes measured and recurrence after PVI in paroxysmal AF patients; and (5) the larger the RAPV in persistent AF patients, the more likely recurrence after PVI becomes.

*Validity of volume and voltage*

We measured 4 volumes (LATV, LACV, RPAV, and LPAV) and bipolar voltage amplitude of the entire LA obtained using high-density 3-dimensional electroanatomical mapping using the PENTARAY catheter. To the best of our knowledge, there have been no previous reports of LA and PV volumes measured separately using the PENTARAY catheter. We evaluated the correlation with the LA volume obtained by contrast CT in the first 15 cases. A significant correlation was found, suggesting that the LA volumes evaluated with the PENTARAY catheter are valid. Compared with data from previous reports of bipolar voltage amplitude of the entire LA measured using a multi-electrode catheter, the mean LA bipolar voltage obtained in our study were similar, suggesting the validity of our measurement<sup>2,11,15</sup>.

### *LA and PV volume expansion*

The size of PV and LA is thought to be a relevant risk factor for AF, post-PVI recurrence, and progression from paroxysmal AF to persistent AF. Previous reports demonstrated that paroxysmal AF patients have greater longitudinal dimensions of LA and larger superior PV volumes than normal control subjects in normal sinus rhythm<sup>6,16-18</sup>). This finding suggests that the larger size of PV and LA is a causative factor of AF or the result of an increment of LA pressure produced by AF.

In our study, we were not able to compare each of the 4 volumes in healthy hearts and paroxysmal AF patients. Therefore, the morphological changes of the LA in paroxysmal AF patients could not be discussed. Nevertheless, all volumes were larger in patients with persistent AF than in those with paroxysmal AF, suggesting that the morphological changes in AF, as previously thought, may involve not only LA volume expansion but also PV volume expansion<sup>5</sup>).

### *Decreased LA bipolar voltage amplitude of persistent AF*

It has been reported that AF with remodeling is associated with low voltage of the LA<sup>5</sup>). Atrial fibrosis has been proposed as one of the processes involved in atrial remodeling<sup>5</sup>). The presence of areas with low voltage in the LA was an independent predictor of AF recurrence after PVI<sup>19</sup>). By contrast, in the present study, we did not observe the low voltage zone below 0.1 mV in LA voltage mapping as previously described. In fact, the LA of persistent AF patients showed a decrease in the voltage amplitude of the entire LA. We speculate that the mechanism of the decrease in LA voltage was owing to the sparsity of the LA muscles and the continuous volume expansion by persistent AF.

### *A predictor of atrial fibrillation recurrence after PVI*

There is clear evidence that enlarged LA dimensions are more frequently observed in patients with AF and that larger LA dimensions are associated with a higher risk of AF recurrence after ablation<sup>20,21</sup>). However, although LA dimensions have been well described in patients with AF, less information is available regarding whether such morphological changes also occur in the PVs<sup>16</sup>). There were no differences in any volume between recurrence and non-recurrence groups in paroxysmal AF. Therefore, LA and PV volumes are not associated with a predictor of AF recurrence after PVI in patients with paroxysmal AF.

In persistent AF, RPAV was significantly larger in the group with recurrent AF after PVI. Previous studies have reported the relationship between AF and PV volume<sup>22-25</sup>). However, this is the first to report a relationship between large RPAV and recurrent AF after PVI. The right PV is close to the atrial septum, which is the longitudinal pillar of the atrial structure. However, the left PV is located on the free wall side and does not have this structure. In previous reports, the presence of a septopulmonary bundle is known as a structural difference between the left and right PVs<sup>26,27</sup>). The septopulmonary bundle is an atrial muscle bundle that runs around the right superior and right inferior PVs. For these reasons, the right PV has a stronger structure than the left PV. The expansion of RPAV is caused by the burden on the LA and

PV to the extent that this strong structure is disrupted, which may explain the high rate of recurrence after PVI in cases with expanded RPAV.

### *Selecting the PV antrum*

In the present study, we divided the LATV into 3 parts at the antrum site. There is no clear anatomical definition of PV antrum, but it refers to the region surrounding the LA-PV junction. The determination of the antrum was dependent on the ablation line. There was no difference in volume by ablation line between the 4 electrophysiologists.

### *Limitations*

This study has several limitations. First, this was a retrospective observational single-center study. Second, the sample size was small and may not be sufficient to detect differences between the groups, particularly because of the low prevalence of recurrence after ablation. Third, the follow-up visits only included electrocardiogram or Holter monitoring, and therefore might have underestimated the recurrence rate of AF. Fourth, there are differences in patient characteristics between the population of this study and the general population. Fifth, there was no control group because we were unable to measure LA and PV of normal subjects. Nevertheless, this study provides an interesting perspective on the invasive treatment of AF. There is a need to increase the number of patients and to clarify the differences in the anatomical and electrophysiological characteristics of persistent and paroxysmal AF in more detail.

### **Conclusions**

We measured 4 volumes and LA bipolar voltage amplitude using the PENTARAY catheter. For all values, those of persistent AF patients were larger than those of paroxysmal AF patients. There was lower LA bipolar voltage amplitude in patients with persistent AF. There was no association between LA volume and recurrence after PVI in paroxysmal AF patients. However, RPAV was larger in the recurrent group of persistent AF patients. Therefore, we determined that larger right PV is a predictor of AF recurrence after PVI in patients with persistent AF. The right PV is close to the atrial septum and the septopulmonary bundle, and the expansion of RPAV reflects the disruption of these structures, which may be involved in this result.

### **Acknowledgments**

We thank all the participants for their patience and cooperation.

### **Conflicts of interest disclosure**

The authors have no conflicts of declare.

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[Received May 7, 2020 : Accepted June 29, 2020]