

# Slow whole left atrial conduction velocity after pulmonary vein isolation predicts atrial fibrillation recurrence

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## Abstract

Background: Atrial conduction velocity may represent atrial fibrillation (AF) substrate after pulmonary vein isolation (PVI). To elucidate the association between whole left atrial conduction velocity (LACV) and AF recurrence after PVI. Methods and Results: This observational study enrolled 279 patients who underwent PVI alone as an initial AF ablation procedure. After PVI, the left atrium was mapped with a 20-pole multielectrode in conjunction with the CARTO3 system during 100-ppm right atrial pacing. Left atrial conduction distance and conduction time were calculated from the start to the end of the propagation wave front in the left atrium. LACVs on the anterior and posterior routes were calculated as conduction distance divided by conduction time. Anterior and posterior LACVs were slower in patients with AF recurrence than in those without (anterior, 0.79 [0.71, 0.86] vs. 0.96 [0.90, 1.06],  $p < 0.001$ ; posterior, 0.99 [0.89, 1.14] vs. 1.10 [1.00, 1.29],  $p < 0.001$ ). AF recurrence was best predicted by anterior LACV with a cut-off value of 0.87 m/s (sensitivity 87%, specificity 81%, and predictive accuracy 84%). Multivariate analysis demonstrated that a slow anterior LACV  $< 0.87$  m/s was an independent predictor of AF recurrence with an adjusted hazard ratio of 11.8 (6.36 – 22.0). Patients with anterior low-voltage areas demonstrated slower anterior LACV than those without low-voltage areas (0.89 [0.71, 1.00] vs. 0.94 [0.87, 1.05],  $p < 0.001$ ). Conclusion: A slow LACV in the entire left atrium was an excellent predictor of AF recurrence after PVI, suggesting the necessity of additional ablations.

## Key words

Atrial fibrillation; pulmonary vein isolation; conduction velocity; fibrosis; low-voltage area

## Abbreviations

AF = Atrial fibrillation; PVI = pulmonary vein isolation; LACV = left atrial conduction velocity

## 2. Introduction

Catheter ablation has become a mainstream treatment option for atrial fibrillation (AF). Electrical pulmonary vein isolation (PVI) is well established as the cornerstone of AF ablation.<sup>1, 2</sup> However, frequent AF recurrence after ablation remains an unsolved problem, with reported 1-year AF recurrence rates of 20-50%.<sup>2-4</sup> Several previous reports suggested that patients with AF recurrence after ablation have a prolonged P-wave duration.<sup>5-7</sup> Atrial conduction disturbance is considered the underlying mechanism of P-wave prolongation, and might be associated with the arrhythmogenic substrate maintaining AF. However, little is known about the impact of endocardial conduction velocity after PVI and remaining arrhythmogenic substrate in the left atrium.

Atrial high-resolution mapping with a 3-dimensional mapping system and multipolar mapping catheter facilitates measurement of whole left atrial conduction velocity (LACV) calculated from a precise conduction

time and distance between two designated points. The purpose of this study was to elucidate the association between LACV and AF recurrence after PVI.

### 3. Methods

#### 3.1. Patients

This observational study enrolled consecutive patients who underwent PVI alone as an initial AF ablation procedure at Kansai Rosai Hospital between March 2017 to November 2018. Patients in whom a voltage map was not obtained due to unstable cardiac rhythm were excluded. Patients with left atrial linear or area ablations were also excluded. This study complied with the Declaration of Helsinki. Written informed consent for the ablation and participation in the study was obtained from all patients, and the protocol was approved by our institutional review board.

#### 3.2. Ablation procedure

Electrophysiological studies and catheter ablation were performed by four experienced operators (M.M, T.K, A.S, and Y.M) with the patient under intravenous sedation with dexmedetomidine. The operator performed the mapping and ablation under guidance with an electroanatomical mapping system (Carto3<sup>®</sup>; Biosense Webster, Diamond Bar, CA, USA).

First, PVI was performed using an open-irrigated ablation catheter (Thermocool SmartTouch<sup>®</sup>, Biosense Webster), a cryoballoon (Arctic Front Advance<sup>®</sup>, Medtronic, Minneapolis, MN, USA), or a laser balloon (HeartLight<sup>®</sup>, CardioFocus, Marlborough, MA, USA). When a radiofrequency catheter was used, a dragging technique was employed to perform circumferential ablation around both ipsilateral pulmonary veins. Radiofrequency energy was applied for 30 s (15 s at the posterior left atrial wall near the esophagus) at each site using a maximum temperature of 42 °C and maximum power of 35 W. Irrigation rate was 17 ml/min. The operator attempted to maintain an appropriate contact force between the catheter and endocardium of 5 to 20 g. In cases using a cryoballoon, 180-sec freezing was applied using a 2nd generation 28-mm cryoballoon catheter. The laser balloon was inflated with the goal of complete occlusion of the PV ostium. Laser lesions were created with a 30–50% lesion overlap. Where very good tissue contact was obtained, maximal power (12 W for 20 seconds) was chosen. At regions with moving blood, laser energy was applied at 7 W for 30 seconds.

PV electrograms were recorded using a 20-pole circular mapping catheter (LassoNaV, Biosense Webster). PVI was considered complete when both entrance and exit blocks were created. If atrial flutters or non-PV AF triggers were observed spontaneously or induced by atrial burst stimuli or isoproterenol infusion, additional ablation were performed.

#### 3.3. Left atrial mapping

Following PVI, detailed voltage mapping using a 20-pole circular catheter with 1-mm electrodes (LassoNaV, Biosense Webster) was performed during 100-beat-per-minute paced rhythm from the high right atrium. Mapping points were automatically acquired using the CARTO Confidence module with the following settings: cycle length filtering,  $\pm 30$  msec; local activation time stability,  $< 3$  msec; position stability,  $< 2$  mm; and density,  $< 1$  mm. Left atrial geometry was conducted in fast-anatomical mapping mode. Mapping was continued to fill all color gaps on the voltage map with an interpolation threshold of 17 mm for the fill threshold and 10 mm for the color threshold. If poor contact between the circular mapping catheter and endocardium surface was suspected, mapping using the ablation catheter was added with a point acquisition setting of contact force [?] 5 g. The band pass filter was set at 30 to 500 Hz.

#### 3.4. Low-voltage area assessment

Low-voltage areas were defined as areas with a bipolar peak-to-peak voltage  $< 0.50$  mV covering  $> 5$  cm<sup>2</sup> of left atrium. On the voltage map, the bipolar voltage color bar was set to range from 0.10 to 0.50 mV and scar level was set at  $< 0.05$  mV. Each low-voltage-area size was manually measured, and the summation of

all low-voltage-area sizes was defined as the low-voltage-area size in the patient. The left atrium was divided into six regions - septal, anterior, roof, posterior, inferior, and posterolateral - as reported previously.<sup>8</sup>

### 3.5. LACV measurement

Left atrial conduction distance and conduction time were calculated from the start to the end of the propagation wave front in the left atrium. LACV was calculated as conduction distance divided by conduction time. An example LACV measurement is presented in Figure 1. Conduction time was the difference in activation time between the start (septum) and end of the propagation wave front (lateral wall) in the left atrium. Conduction distance was measured manually by tracing the pathway of the propagation wave front from the start point to the end point in the left atrium. The pathways of the propagation wave front were classified into anterior and posterior routes. The anterior route originates at the septum, crosses the anterior wall toward the appendage, passes over the left atrial appendage orifice, and finally reaches the lateral mitral annulus, where superior- and inferior-direction propagation waves collide and disappear. The posterior route goes toward the superior left atrium (roof) from the septal propagation origin, then goes downward on the posterior wall, turns below the left inferior pulmonary vein, and reaches the lateral mitral annulus.

Reproducibility of the LACV was assessed. Interobserver variability for anterior and posterior LACV was 0.025 m/s, calculated in 10 randomly selected patients as the difference in 2 measurements in the same patient by 2 different observers. There was no difference in anterior (0.88 [0.81, 1.06] vs. 0.88 [0.80, 1.06]  $p=0.86$ ) or posterior LACV values (1.08 [0.86, 1.23] vs. 1.07 [0.85, 1.23],  $p = 0.55$ ) between 2 examiners.

### 3.6. Post-procedure follow-up

Patients were discharged two days after ablation if their clinical status was stable. Following a blanking period of 3 months, they completed outpatient clinic visits and 12-lead ECG monitoring at 1, 3, 6 and 12 months, and 24 h-Holter ECG monitoring every 6 months. Additional Holter monitoring was performed if arrhythmic symptoms occurred. Either of the following events following the initial 3 months after ablation (blinking period) was considered to indicate AF recurrence: (1) atrial tachyarrhythmias recorded on routine or symptom-triggered ECG during an outpatient visit; or (2) atrial tachyarrhythmias of at least a 30 seconds' duration on ambulatory ECG monitoring. All antiarrhythmic drugs were discontinued 3 months after the procedure, unless AF recurrence was diagnosed.

### 3.7. Statistical analysis

Categorical values are expressed as absolute values and relative frequencies. Continuous variables are expressed as mean  $\pm$  SD. Tests for significance were conducted using the unpaired t-test or nonparametric test (Mann-Whitney U-test) for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. When a continuous LACV significantly differed between the two groups, receiver operating characteristic analysis was performed to delineate the cut-off points. Univariate and multivariate Cox proportional hazard models and logistic regression analyses were used to determine the clinical factors that were associated with AF recurrence and a slow LACV, respectively. Survival rates free from atrial tachyarrhythmias were calculated using the Kaplan–Meier method. Survival curves between groups were compared with the two-sided Mantel–Haenszel (log-rank) test. All statistical analyses were performed using commercial software (SPSS version 25 (r), SPSS, Chicago, IL, USA), and statistical significance was defined as  $P < 0.05$ .

## 4. Results

### 4.1. Patient characteristics

Patient characteristics are shown in Table 1. During a mean follow-up period of 436 $\pm$ 188 days, 68 (24%) patients experienced AF recurrence. Patients with AF recurrence more frequently had the persistent type of AF and a larger left atrial diameter. Procedural characteristics are shown in Table 2. PVI was completed in all patients, and no severe procedure-related complications such as cardiac tamponade, stroke, esophageal

injury, or major bleeding were observed. Patients with AF recurrence had a longer procedure time, higher frequency of cryoballoon usage, and more mapping points on the voltage map after PVI.

## 4.2. LACV and AF recurrence

LACVs, conduction times, and conduction distances between patients with and without AF recurrence are compared in Figure 2. Left atrial conduction time was longer, and anterior and posterior LACVs were slower in patients with AF recurrence than in those without. The anterior route demonstrated a shorter distance and slower LACV than the posterior route irrespective of AF recurrence. Anterior and posterior LACVs showed moderate linear correlation ( $R = 0.70$ ,  $p < 0.0001$ ; supplementary figure 1). ROC curve analysis demonstrated that anterior LACV with a cut-off value of 0.87 m/s best predicted AF recurrence, with sensitivity of 87%, specificity of 81%, and predictive accuracy of 84% (Supplementary figure 2). AF-recurrence-free rate was significantly lower in patients with a slow anterior LACV  $< 0.87$  m/s than in those with an LACV  $\geq 0.87$  m/s (Figure 3). Example cases of normal and slow LACV are presented in the supplementary movie. Multivariate analysis incorporating baseline characteristics and left atrial mapping data revealed that a slow anterior LACV of  $< 0.87$  m/s was the only independent predictor of AF recurrence, with a hazard ratio of 11.8 (6.36 – 22.0) (Table 3). AF recurrence-free rate was significantly higher in patients with an anterior LACV  $< 0.87$  m/s than in those with  $\geq 0.87$  m/s. Clinical factors associated with a slow anterior LACV ( $< 0.87$  m/s) are explored in Supplementary table. Female, persistent AF, and large left atrium were related to a slow anterior LACV. Multivariate analysis revealed that female gender was the only independent predictor of having a slow anterior LACV.

## 4.3. LACV and low-voltage area

Low-voltage areas were more frequently observed in patients with AF recurrence than in those without (Table 2). In addition, among patients with low-voltage areas, the low-voltage-area size was larger in patients with AF recurrence than in those without. Figure 4 shows a comparison of LACVs between patients without low-voltage areas, with low-voltage areas limited to the region where the propagation wave did not pass (ex-situ), and with low-voltage areas existing across the propagation-wave route (in-situ). LACV on the anterior route was lower in patients with in-situ (anterior) low-voltage areas than in those without low-voltage areas. In contrast, posterior LACV was not associated with the presence of low-voltage areas.

## 5. Discussion

This observational study in 279 patients who underwent initial AF ablation investigated the association between LACV and AF recurrence. Three main findings were obtained: a slow LACV on both anterior and posterior routes was significantly associated with AF recurrence; an anterior LACV  $< 0.87$  m/s independently predicted AF recurrence; and patients with low-voltage areas in the anterior regions demonstrated a slower anterior LACV. The finding that a slow LACV in the entire left atrium is an excellent predictor of AF recurrence after PVI suggests the necessity of additional ablations. To our knowledge, this is the first clinical study to investigate the association between LACV and AF recurrence.

### 5.1. Histological insights into LACV slowing

The main determinants of myocardial conduction velocity are inter-cellular gap junction function and intracellular depolarization. These are in turn considered to be influenced by tissue fibrosis:<sup>9-11</sup> Myocardial tissue with interstitial fibrosis is reported to demonstrate gap junction remodeling, including the depletion and abnormal distribution of gap junctions, which result in conduction disturbance.<sup>9</sup> Moreover, myocardial fibrosis promotes myocyte-myofibroblast coupling and elevates myocyte resting membrane potential, causing conduction velocity to decrease by inhibiting the depolarization process of cell membrane.<sup>10</sup> In addition, an elevated membrane potential may shorten action potential duration and refractory period. Finally, both conduction disturbance and a short refractory period likely contribute to the development of reentrant circuits and AF persistence.<sup>11</sup>

### 5.2. Slow LACV as a marker of left atrial AF substrate

In this study, we found that a slow anterior LACV more accurately predicted AF recurrence than any other previously reported predictor, including AF type, left atrial size, and low-voltage-area existence. This excellent predictive value of a slow LACV might be explained as follows. First, conduction slowing is a direct measure of factors associated with arrhythmia with the reentrant mechanism, such as rotor during AF,<sup>12-14</sup> and slow conduction zone during regular atrial tachycardia.<sup>15</sup> Second, as described in the above paragraph, conduction slowing is a likely consequence of atrial fibrosis, which could also provoke shortening of the refractory period and triggered activity. Thus, a slow LACV possibly represents a variety of electrophysiological characteristics which in concert render the subject vulnerable to AF development. Third, this study measured LACV from the start to the end of the left atrial propagation wave front, which facilitates comprehensive assessment of left atrial arrhythmogenicity. Anterior LACV was slower than posterior LACV, irrespective of the presence of AF recurrence. A physiological slow anterior LACV would be partially attributable to conduction slowing of the anterior propagation wave perpendicularly crossing the septo-pulmonary bundle.<sup>16</sup> In addition, LACV slowing on the anterior route more precisely predicted AF recurrence than that on the posterior route. Left atrial fibrosis would progress initially in the anterior-septal region before other regions, as reported in previous studies which showed that low-voltage areas most commonly existed in the anterior-septal region.<sup>8, 15</sup> Several studies have assessed atrial conduction disturbance using P-wave duration obtained by surface signal-averaged electrocardiogram,<sup>5-7</sup> and found that P-wave prolongation was associated with AF recurrence after PV. These results suggest that inter- and intra-atrial conduction disturbances represent an arrhythmogenic substrate of AF. Our present study using a recently available high-density mapping system confirms these previously reported findings.

### 5.3. LACV and low-voltage area

Patients in the present study with low-voltage areas had a slower LACV than those without. Previous studies reported that local conduction velocity in low-voltage areas was significantly slower than that in preserved-voltage areas.<sup>17</sup> Conduction slowing and low voltage are therefore likely different manifestations of the same pathophysiological phenomenon, such as fibrosis.<sup>9, 10, 18</sup> Of note, this study showed that a slow anterior LACV was a better predictor of AF recurrence than the existence of low-voltage areas. The bipolar voltage and extent of a low-voltage area could be markedly influenced by any of several factors, such as the mapping catheter used (electrode profile) and catheter orientation in relation to propagation direction.<sup>19, 20</sup> One advantage of LACV measurement is that it provides a comprehensive assessment of all mapping points, and is less dependent on individual electrogram signals. As a result, LACV values measured in one electrophysiological laboratory using a specific mapping catheter might be universally reproducible in other laboratories using different mapping catheters.

### 5.4. Clinical Implication

LACV provides excellent prediction for AF recurrence after PVI. This information will likely enable the differentiation of patients who need additional left atrial ablation other than PVI from the majority of patients who do not experience AF recurrence with PVI alone. Nevertheless, LACV as measured in this study does not identify those specific diseased areas whose ablation would improve rhythm outcomes. Future studies are needed to explore the best ablation strategy in patients with a slow LACV.

## 6. Limitations

Several limitations of the present study warrant mention. First, LACV measurement was done by a single medical engineer, possibly resulting in biased data, albeit that inter-observer variability was 0.025 m/s, which we assume to be sufficiently low. Second, the study did not investigate data from repeat procedures, and did not examine the reconnection rate of isolated pulmonary vein. Accordingly, AF recurrence does not necessarily mean that the patient had an extra-pulmonary-vein AF substrate. Third, we did not perform right atrial mapping, although the right atrium is also thought to play a role in AF development, in some patients at least. Fourth, AF recurrence after discharge was quantified on the basis of intermittent short-time ECG and symptom-triggered ECG, giving rise to the possibility that asymptomatic episodes of AF might have been missed. Finally, the study was conducted under a single center, observational design. Confirmation

awaits a prospective multicenter study.

## 7. Conclusion

A slow LACV in the entire left atrium is an excellent predictor of AF recurrence after PVI, and suggests the necessity of additional ablations.

## Disclosure

None.

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## Figure legend

### Figure 1. LACV measurement

LACV was calculated by dividing left atrial conduction distance by conduction time. Conduction time was defined as the difference in activation time between the start (septum) and end of the propagation wave front (lateral wall) in the left atrium. Conduction distance was measured manually by tracing the pathway of the propagation wave front from the start point to the end point in the left atrium. The pathways of the propagation wave front were classified into anterior and posterior routes. The anterior route originates at the septum, crosses the anterior wall toward the appendage, passes over the left atrial appendage orifice, and finally reaches the lateral mitral annulus, where superior- and inferior-direction propagation waves collide and disappear. The posterior route goes toward the superior left atrium (roof) from the septal propagation origin, then downward on the posterior wall, turns below the left inferior pulmonary vein, and reaches the lateral mitral annulus. LACV, left atrial conduction velocity; LAT, local activation time.

### Figure 2. LACV, distance, and time

Left upper panel compares left atrial conduction velocities (LACVs) (A). Anterior and posterior LACVs were slower in patients with AF recurrence than in those without. Anterior route showed slower conduction velocity than the posterior route, irrespective of AF recurrence. Right upper panel compares left atrial conduction distances (B). The anterior route demonstrated shorter distance irrespective of AF recurrence. Left lower panel compares left atrial conduction time (C). Patients with AF recurrence had a longer conduction time than those without. LACV, left atrial conduction velocity; AF, atrial fibrillation.

### Figure 3. AF recurrence-free survival curves

AF recurrence-free rate was significantly lower in patients with a slow LACV of  $< 0.87$  m/s than in those with an LACV of  $\geq 0.87$  m/s. LACV, left atrial conduction velocity; AF, atrial fibrillation.

### Figure 4. Comparison of LACV with and without low-voltage areas

Left atrial conduction velocities (LACVs) were compared between patients without low-voltage areas, with low-voltage areas limited to areas where the propagation wave did not pass (ex-situ), and with low-voltage areas existing across the propagation-wave route (in-situ). LACV in the anterior route was lower in patients with in-situ (anterior) low-voltage areas than in those without low-voltage areas. In contrast, posterior LACV was not associated with the presence of low-voltage areas. LACV, left atrial conduction velocity.

### Supplementary figure 1 Correlation between anterior and posterior LACVs

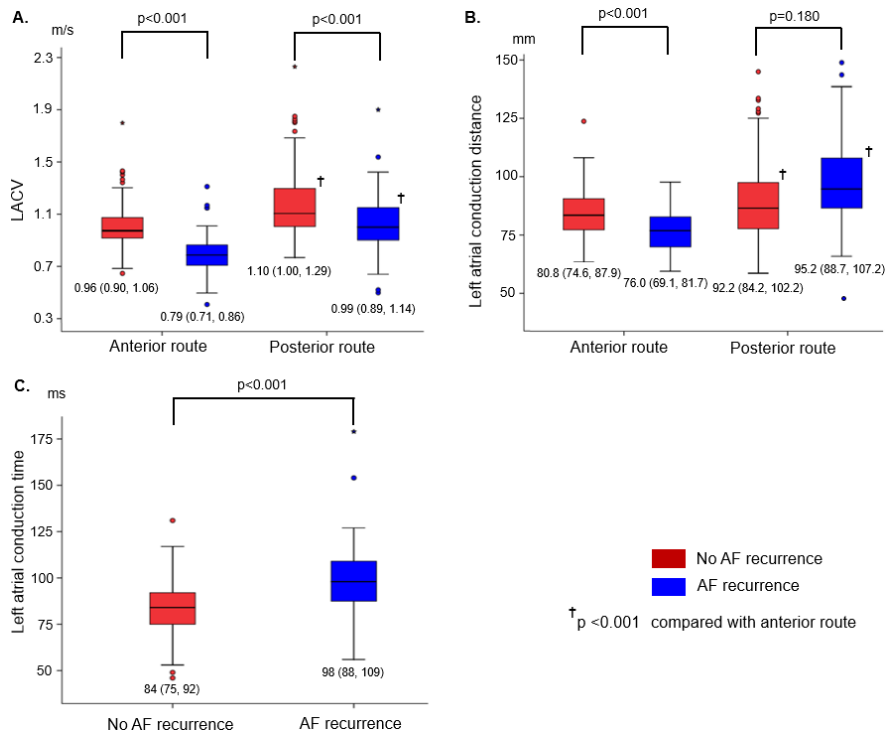
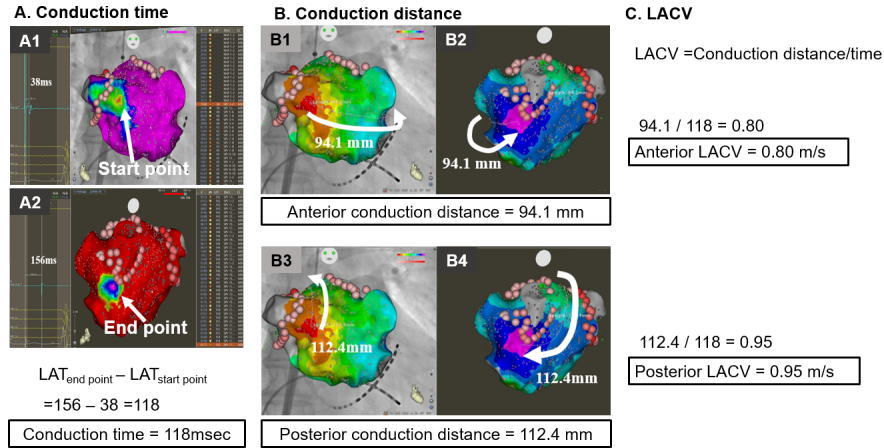
Both LACVs demonstrated a moderate correlation. LACV, left atrial conduction velocity.

**Supplementary figure 2. Receiver-operating characteristic curves for the prediction of AF recurrence**

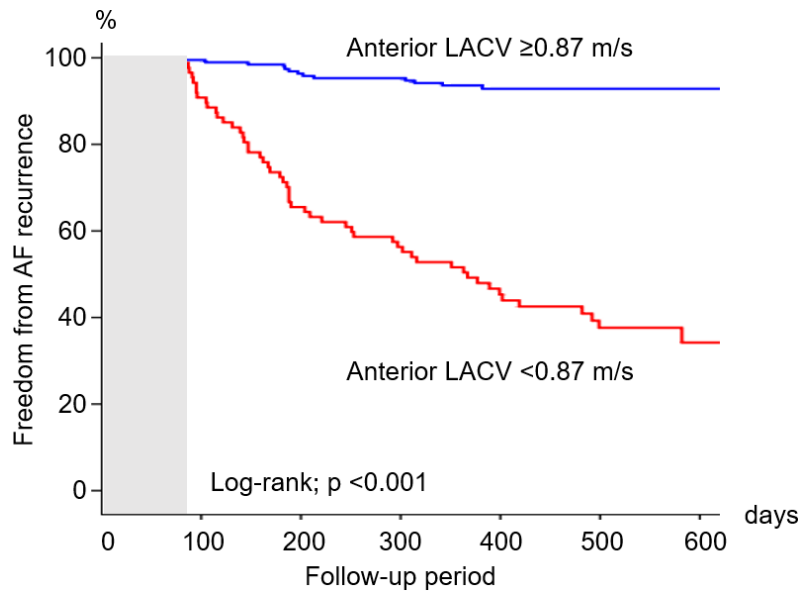
Receiver operating characteristic analysis was performed to delineate cut-off points for the prediction of AF recurrence. Anterior LACV had the highest AUC. LACV, left atrial conduction velocity; AUC, area under the curve; AF, atrial fibrillation.

**Supplementary movie. Examples of normal and slow LACVs.**

Examples of normal (Case 1) and slow LACV (Case 2) are presented. LACV, left atrial conduction velocity.







LACV $\geq 0.87$ m/s	192	191	184	173	109	82	41
LACV $< 0.87$ m/s	87	79	57	48	34	23	7

