1. Introduction

Catheter-based pulmonary vein isolation (PVI) has become a widely accepted means of treating symptomatic drug-refractory atrial fibrillation (AF)\(^1\). In cases of persistent AF (PerAF), PVI is not always successful without ablation at sites of complex fractionated atrial electrograms (CFAEs) and high dominant frequency (DF) and/or multiple linear ablation\(^2\)–\(^5\). A recent study, however, showed no reduction in the AF recurrence rate when either ablation of CFAEs or linear ablation was performed in addition to PVI in patients with PerAF\(^6\). Pre-existent left atrial (LA) scars indicated by low-voltage zones (LVZs) on 3-dimensional (3D) electroanatomic maps are implicated in suboptimum ablation outcomes\(^7\), \(^8\), and success has been achieved in patients with PerAF when, in addition to PVI, the atrial substrate has been modified by ablation of low-voltage areas detected during sinus rhythm (SR)\(^9\)–\(^13\). Slight differences exist between the definitions of such low-voltage zones (LVZs), which are described variously as areas of bipolar voltage of < 0.4 mV \(~< 0.5\) mV, depending on the group of investigators\(^14\)–\(^16\).

It is difficult to maintain SR in patients with PerAF, and thus LA voltages recorded during AF that may actually reflect LVZs that exist during SR have not been reported. We have reported significant correlation between LA voltage during SR and that during AF\(^17\). Thus, we hypothesized that LVZs that exist during AF can be used to identify LVZs that exist during SR. Therefore, we conducted a study to test this hypothesis.

2. Materials and methods

2.1 Study patients

Included in the study were 8 patients (5 men, 3 women; mean age 66.5 \(\pm\) 4.9 years) scheduled for their first catheter ablation of AF and in whom scarring (bipolar voltage < 0.5 mV during SR) existed in at least 1 of 7 LA segments. Four of the patients had paroxysmal AF (PAF; AF lasting less than 7 days), and 4 had PerAF (AF lasting 7 days or more). None of the patients had cardiomyopathy, valvular heart disease, or congenital heart disease. Adequate oral anticoagulation therapy was administered for at least 1 month before the ablation procedure, and all antiarrhythmic drugs were discontinued for at least 5

**Background:** As we have found a significant correlation between left atrial (LA) voltage during sinus rhythm (SR) and that during atrial fibrillation (AF), we hypothesized that the existence of low-voltage zones (LVZs) during AF can be used to identify LVZs during SR. Therefore, we conducted a study to test this hypothesis.

**Methods:** In 8 patients, high-density bipolar voltage mapping (> 300 points) of the left atrium was performed with a 20-pole circular catheter with 4-4-4-mm interelectrode spacing. The left atrium was divided into 7 segments, and the mean LA bipolar voltages recorded over 5 seconds during SR and AF were determined by measurement of the peak-to-peak amplitudes.

**Results:** LVZs identified at each segment were compared between SR and AF. LA bipolar voltages obtained during SR and AF correlated positively (\(r = 0.74, p < 0.0001\)). With the low voltage during SR defined as < 0.5 mV, the low voltage of < 0.2 mV during AF approximately matched the low LVZs mapped during SR.

**Conclusions:** These findings indicate that LVZs of < 0.5 mV during SR could be predicted from LVZs identified during AF by designating a threshold AF voltage of 0.2 mV.

**Key words:** catheter ablation, atrial fibrillation, sinus rhythm, left atrium, low-voltage zone

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half-lives before the procedure. Transesophageal echocardiography and transthoracic echocardiography were performed upon admission for determination of maximum LA volume (by the prolate-ellipsoid method) and left ventricular ejection fraction (by the Teichholz method). The study protocol was approved by the Institutional Review Board of Nihon University Itabashi Hospital (May 25, 2016; RK-160614-10), and all patients provided written informed consent for their participation.

2.2 Electrophysiologic study
Electrophysiologic study was performed in all patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl, as described previously. After vascular access was obtained, a single transseptal puncture was performed, and intravenous heparin was administered to maintain an activated clotting time of more than 300 seconds. After 2 long sheaths (1 SL0 sheath and 1 Agilis sheath; St. Jude Medical, Inc., St. Paul, MN, USA) were inserted into the left atrium via a transseptal puncture, the 3D geometry of the left atrium and 4 pulmonary veins (PVs) was reconstructed with the use of an EnSite NavX Classic system (St. Jude Medical, Inc.) and a 20-pole circular mapping catheter with 4-4-4-mm interelectrode spacing (AFocus II catheter, St. Jude Medical, Inc.). We recorded multiple bipolar signals (filter setting: 30–300 Hz) from the AFocus II catheter with the EnSite Velocity Cardiac Mapping System (St. Jude Medical, Inc.). If the patient was in SR, AF was induced by rapid atrial pacing from the coronary sinus ostium, and bipolar signals were recorded 5 minutes after AF induction, and if the patient was in AF, SR electrograms were recorded after cardioversion.

2.3 Segmentation of the left atrium and recording of bipolar electrograms
The left atrium was divided into 7 segments (anterior wall, septum, roof, appendage, posterior wall, floor, mitral isthmus, mitral isthmus), and mean bipolar atrial electrogram amplitudes (filter setting: 30–300 Hz) were compared for each segment (Fig. 1). Nineteen bipolar electrograms (1-2 … 19-20) from the 20-pole circular electrodes with 4 mm spacing were recorded simultaneously with an AFocus II 20-pole dual ring catheter for a single beat during SR and for 5 seconds during AF, and high-density 3D electroanatomic mapping (> 300 signals) of the entire left atrium was performed. Single-beat peak-to-peak bipolar voltages during SR were measured, and peak-to-peak bipolar voltages during AF were averaged from the 5-second recordings at 5 points within each LA segment. The 5 points at which the recordings were obtained in each segment during SR and AF were located within 3 mm of each other on the 3D LA map.

Bipolar electrogram amplitudes were measured during AF and SR, and low voltage was defined as < 0.5 mV during SR and < 0.2 mV during AF.

2.4 Data analysis
Voltages recorded for the total patients during SR and AF are expressed as mean ± SD values. Correlation between voltages recorded during SR and AF was tested by Pearson’s correlation coefficient. Association between scarring identified during SR and scarring identified during AF was tested by Fisher’s exact test. In addition, sensitivity, specificity, the positive predictive value, negative predictive value, and predictive accuracy of AF voltage for detection of low voltage during SR were tested. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC, USA), and p < 0.05 was considered significant.

3. Results
3.1 Patients’ baseline clinical and echocardiographic characteristics
The clinical and echocardiographic characteristics of the 8 study patients are shown on Table 1. Fifty percent of the patients were PAF and 50% of the patients were PerAF.

Fig. 1 Left atrium (LA) divided into 7 regions.
①–anterior wall, ②–septum, ③–roof, ④–appendage, ⑤–posterior wall, ⑥–floor, ⑦–mitral isthmus
LA voltages recorded during SR and AF

LA voltages recorded at each LA segment during SR and AF correlated positively (r = 0.74, p < 0.0001), and mean bipolar voltages recorded during AF were approximately one-third of the bipolar voltages recorded during SR.

LVZs and scarring identified at the LA segments during SR and AF

Electroanatomic maps acquired during SN and during AF that depicted LVZs and areas scarring are shown for each patient in Fig. 3. Grey color shows scar (< 0.2 mV) area during AF (left panel in each patient) and purple color shows no LVZ (> 0.5 mV) area during SR (right panel in each patient). SR voltage < 0.5 mV vs. AF voltage < 0.2 mV was recorded at a total of 12 segments; SR voltage < 0.5 mV vs. AF voltage > 0.2 mV was recorded at a total of 3 segments; SR voltage > 0.5 mV vs. AF voltage < 0.2 mV was recorded at a total of 10 segments; and SR voltage > 0.5 mV vs. AF voltage > 0.2 mV was recorded at a total of 31 segments. Sensitivity, specificity, positive predictive value, negative predictive value, and predictive accuracy of AF voltage < 0.2 mV for identifying SR voltage < 0.5 mV were 88%, 74%, 75%, 91%, and 77%, respectively.

4. Discussion

4.1 Major finding

Our important study finding is that LVZs, i.e., areas of < 0.5 mV, during SR could be predicted from areas of < 0.2 mV during AF.

4.2 LA voltages during SR and AF

In patients with AF, areas of low bipolar voltage recorded during SR constitute a substrate abnormality that progresses in parallel with the progression of AF. Low voltage in the left atrium, consistent with pre-existent scarring, has been shown to be a powerful predictor of procedural failure in patients undergoing PVI for AF. Recent studies have shown that, in comparison to conventional PVI, PVI with the addition of voltage-guided substrate modification achieved by targeting the low-voltage area is more effective, is safer, and leads to lower proarrhythmic potential. A measurement of < 0.5 mV was used in several previous studies as the criterion for identifying low-voltage areas indicative of interstitial fibrosis in the right and left atria in the setting of SR or atrial pacing. Furthermore, both Malcolm-Lawes et al. and Oaks et al. showed that LA voltage < 0.5 mV during SR corresponds to LA fibrosis identified by delayed

| Table 1 Baseline clinical and echocardiographic characteristics of the 8 study patients. |
|---------------------------------|------------------|-----------------|-------------------|------------------|-----------------|-----------------|
| Age (years)                    | 66.5 ± 4.9       | Sex; male       | 5 (62.5)          | PAF               | 4 (50)          |
| AF duration (months)           | 13.5 (9.0–51.0)  | Body mass index, kg/m² | 25.6 ± 4.6    | Hypertension      | 4 (50)          |
| Diabetes mellitus              | 1 (12.5)         | Heart failure   | 0 (0)             | LVEF (%)          | 72.3 ± 5.7      |
| Echocardiographic measures     |                 | LAD, mm         | 40.4 ± 7.0        |                  |                 |
| Values are shown as mean ± SD, median (and interquartile range), or n (%). |
| AF – atrial fibrillation, PAF – paroxysmal atrial fibrillation, LVEF – left ventricular ejection fraction, LAD – left atrial diameter. |

4.2 LA voltages during SR and AF

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Fig. 2 Bar graph showing voltages obtained at each of the left atrial segments during sinus rhythm (SR) and atrial fibrillation (AF).
Fig. 3  Patients’ three-dimensional electroanatomic maps showing low-voltage areas in each LA segment. Upper images are antero-posterior views and lower images are postero-anterior views. Images at the left show low-voltage areas during atrial fibrillation; grey areas are areas of bipolar voltage < 0.2 mV (scarred areas). Images at the right show low-voltage areas during sinus rhythm; purple areas are areas of bipolar voltage ≥ 0.5 mV (non-low-voltage areas).
enhancement magnetic resonance imaging (MRI)\textsuperscript{17, 18}. Although immediate recurrence of AF after cardioversion often occurs in patients with PerAF, regardless of whether the PerAF is long-lasting, voltages demarcating normal and abnormal tissue during ongoing AF have not been established. Previous studies have shown positive point-by-point correlation between bipolar voltage during SR and that during AF\textsuperscript{19-23}. However, even compared with the same point, the correlation of left atrial voltage between SR and AF showed wide variation, furthermore, compared with different mapping points, more wide variation exists\textsuperscript{19, 21}. Fiala et al. arbitrarily set a cut-off value of 0.2 mV to identify sites that might anatomically correspond to areas of advanced interstitial fibrosis\textsuperscript{29}. For ablation targeting low-voltage areas in patients with PerAF, Jadidi et al. defined LA low bipolar voltage as < 0.5 mV measured peak-to-peak from 2 consecutive AF beats\textsuperscript{13}. However, Qureshi et al. showed that mean of 10–15 AF cycle lengths was needed to settle a stable AF voltage\textsuperscript{20}, and they studied low-voltage regions identified during AF vs. SR by means of MRI, reporting voltages of 0.25 ± 0.18 mV and 0.59 ± 0.36 mV for late-gadolinium enhanced and non-late-gadolinium enhanced areas, respectively\textsuperscript{25}. In the present study, AF voltages were calculated as the mean values on 5-second recordings. Results we obtained based on qualitative analysis were similar to those of Qureshi et al.\textsuperscript{25}. Direction-dependent changes in bipolar voltages and electrogram fractionation during sinus rhythm, high right atrial pacing, and distal coronary sinus pacing\textsuperscript{26-28}. Therefore, spatio-temporal changes in wave-front direction during AF might relate to the lower amplitude of the local bipolar voltages during AF.

### 4.4 Study limitations

The study was limited by the small number of patients. Therefore, we did not calculate the Receiver Operator Characteristic Curve in the present study. In addition, low voltage at each LA segment was estimated visually, and the points, at which voltages were acquired during SR and AF, although probably adjacent, were not identical because SR and AF voltage maps were created separately.

### 5. Conclusions

Results of our study indicate that LVZs of < 0.5 mV during SR could be predicted from LVZs identified during AF by designating 0.2 mV as the threshold AF voltage.

### Conflict of interest

All authors report no financial conflicts of interest.

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