



Original Article

Left atrial remodeling: Regional differences between paroxysmal and persistent atrial fibrillation

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ABSTRACT

Background: The mechanisms underlying self-perpetuation of persistent atrial fibrillation (AF) are not well understood. To gain insight into these mechanisms, we conducted a study comparing left atrial (LA) electroanatomic maps obtained during sinus rhythm between patients with paroxysmal AF (PAF) and patients with persistent AF (PerAF).

Methods: The study included 23 men with PAF (age, 56.3 ± 12.1 years) and 13 men with PerAF (age, 54.3 ± 13.4 years). LA voltage mapping was performed during sinus rhythm. The clinical and electroanatomic characteristics of the two groups were evaluated and analyzed statistically.

Results: The bipolar voltages at the LA septum, roof, and posterior wall, right superior pulmonary vein (PV) and its antrum, right superior PV carina, and right inferior PV antrum were significantly lower in patients with PerAF than in those with PAF. The bipolar voltages in other parts of the LA did not differ statistically between the two groups.

Conclusion: PAF and PerAF seem to be characterized by differences in the regional voltage in the LA and PVs. The LA structural remodeling of PerAF may initiate from the right PVs and their antra and LA septum, roof, and posterior wall.

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1. Introduction

It is widely accepted that atrial fibrillation (AF) arises as a result of a complex interaction among the initial trigger, substrate, and perpetuators [1]. It has been shown experimentally that the shortened effective refractory period (ERP) and slowed conduction that result from AF promote continuance of the AF, leading to the concept that “AF begets AF” [2]. Indeed, this paradigm appears to be relevant in both paroxysmal AF (PAF) and persistent AF (PerAF) [1]. Although experimentally induced sustained AF has been shown to lead mainly to structural changes in the atrial myocytes [3], the atrial substrate in patients with PAF and in those with PerAF has not been well characterized. Prior studies have shown that the left atrial (LA) voltage was lower in patients with PerAF than in those with PAF [4–6]; however, the regional distribution of

LA voltage has not been fully evaluated in either patients with PAF or PerAF. Thus, we conducted a study to compare the regional differences in the LA voltage between patients with PAF and PerAF.

2. Material and methods

2.1. Study patients

The study included 23 and 13 patients undergoing radio-frequency ablation for PAF and PerAF, respectively. All patients were men aged 55.6 ± 12.4 years. Patients with structural heart disease or valvular heart disease were not included in the study so that the potential influence of these diseases on atrial remodeling would be avoided. Patients who had undergone a prior AF ablation procedure were also excluded from the study. In addition, patients with left ventricular (LV) dysfunction (LV ejection fraction [EF] < 50%), coronary artery disease, severe obstructive apnea, or poorly controlled hypertension associated with a significant echocardiographically determined LV hypertrophy (myocardial

Abbreviations: PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; LA, left atrium; PV, pulmonary vein; ERP, effective refractory period.

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wall thickness > 1.1 cm) were excluded. AF was defined as paroxysmal when episodes lasted < 7 days and self-terminated and as persistent when episodes lasted > 7 days [7]. The study protocol was approved by the Human Research Ethics Committee of Nihon University Itabashi Hospital (May 25, 2016; RK-160614-10), and all patients provided written informed consent for their inclusion in the study.

2.2. Electrophysiological study

All study patients were maintained on anticoagulation therapy for at least 1 month before the ablation procedure, with a target international normalized ratio of 2.0–3.0 for those who were administered warfarin. Antiarrhythmic medications were stopped for at least 5 half-lives before the procedure. All patients underwent transesophageal echocardiography 1 day before the procedure to rule out the possibility of LA thrombus. Electrophysiological study and ablation were performed under conscious sedation achieved with propofol and fentanyl. The surface electrocardiogram and endocardial electrogram findings were monitored and stored in a digital electrophysiology recording system (BARD LabSystem Pro, Murray Hill, NJ, USA). The intracardiac electrograms were filtered at 30–250 Hz and measured at a sweep speed of 100–200 mm/s. The LA was accessed via a transseptal puncture, and a heparin bolus was administered to achieve a target activated clotting time (ACT) of > 300 s.

2.3. Electroanatomic mapping

The electrophysiological study was performed in all patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl. After obtaining vascular access, a single transseptal puncture was created, and intravenous heparin was administered to maintain an ACT of > 300 s. After inserting two long sheaths (1 SLO sheath and 1 Agilis sheath; St. Jude Medical, Inc., St. Paul, MN, USA) into the left atrium via the transseptal puncture, the three-dimensional (3D) geometry of the left atrium and the 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 from adjacent electrode pairs (1–2, 2–3, 19–20; filter setting: 30–300 Hz) simultaneously during sinus rhythm (SR). If the patients had AF, SR electrograms were recorded after cardioversion. A bipolar electrogram amplitude of < 0.5 mV was identified as a low voltage, and that of ≥ 1.5 mV was identified as

a normal voltage. More than 400 location points per patient and at least > 30 points per segment were recorded for each patient.

2.4. LA/PV segmentation

The left atrium and PVs were divided into 16 segments: LA anterior wall, LA septum, LA floor, LA posterior wall, LA roof, and LA appendage; right superior PV (RSPV), RSPV antrum, right PV (RPV) carina, right inferior PV (RIPV), and RIPV antrum; and left superior PV (LSPV), LSPV antrum, left PV (LPV) carina, left inferior PV (LIPV), and LIPV antrum (Fig. 1). The PV antrum was defined as the area where a unique potential with double deflections (LA and PV potentials) could be documented between the PV ostium and LA body. The PV ostium was identified as the point of maximal inflection between the PV wall and LA wall. The carina was defined as the area between the superior PV antrum and inferior PV antrum.

For each of the 16 segments, bipolar electrogram amplitudes were compared between patients with PAF and those with PerAF. The mean bipolar voltage was calculated for each segment.

2.5. Statistical analysis

The study variables were presented as mean \pm SD values or numbers and percentages of the patients. Between-group differences in the continuous variables were analyzed using the Mann-Whitney U test. All statistical analyses were performed using the StatView 5.0 software (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered significant.

3. Results

3.1. Patients' clinical characteristics

The patients' clinical characteristics and indices of cardiac function are summarized in Table 1. There was no significant difference in age or sex ratio between the PAF group and PerAF group. AF duration was significantly longer in the PerAF group than in the PAF group. A history of heart failure (\geq NYHA Class III) was significantly more prevalent in the PerAF group than in the PAF group. LA diameter, LA volume, and LV end-systolic and end-diastolic dimensions were significantly greater in the PerAF group than in the PAF group. The LVEF did not differ significantly between the two groups.

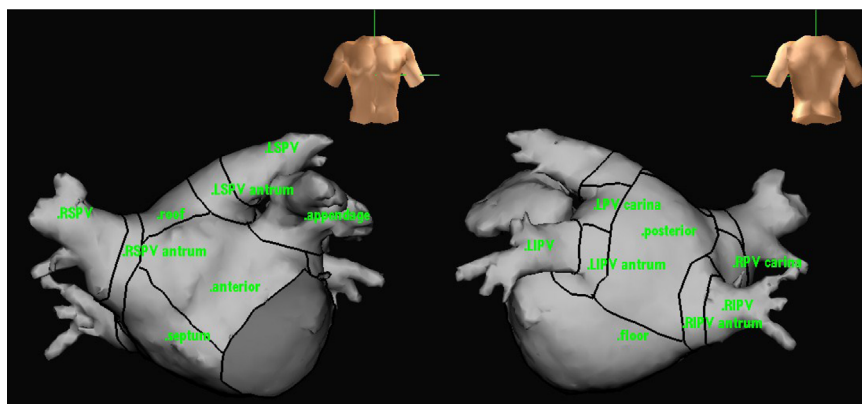


Fig. 1. Anatomical regions of the left atrium (LA) and pulmonary veins (PVs). LA body: roof, anterior wall, posterior wall, interatrial septum, and floor; Right PVs: right superior (RS) PV, RSPV antrum, right (R) PV carina, right inferior (RI) PV, and RIPV antrum; left PVs: left superior (LS) PV, LSPV antrum, left (L) PV carina, LIPV, and LIPV antrum; and LA appendage.

Table 1
Clinical characteristics of the total study patients and of each group.

	Total patients (n=36)	PAF group (n=23)	PerAF group (n=13)	p value PAF vs PerAF
Age (years)	55.6 ± 12.4	56.3 ± 12.1	54.3 ± 13.4	0.6603
Sex ratio (M/F)	36/0	23/0	13/0	1.0000
AF duration (days)	1460 (120–7300)	1080 (90–2920)	1530 (120–7300)	0.0452
Body mass index (kg/m ²)	23.8 ± 3.2	23.4 ± 2.1	23.4 ± 1.5	1.0000
Casual factors				
Hypertension	13 (39.4)	9 (40.9)	4 (36.4)	0.6159
Diabetes mellitus	4 (12.1)	2 (9.1)	2 (18.2)	0.5396
Prior stroke	1 (3.0)	1 (4.5)	0 (0.0)	58130.
Heart failure	5 (15.2)	1 (4.5)	4 (36.4)	0.0163
Indices of cardiac function ^a				
LAD (mm)	39.8 ± 7.3	36.8 ± 5.6	43.8 ± 7.5	0.0127
LAV (cm ³)	49.3 ± 23.0	39.4 ± 15.7	62.9 ± 24.1	0.0064
LVDd (mm)	49.0 ± 6.2	46.4 ± 5.6	52.1 ± 5.7	0.0167
LVDs (mm)	32.3 ± 6.9	29.0 ± 5.1	36.1 ± 7.2	0.0074
LVEF (%)	64.3 ± 11.2	67.5 ± 6.9	59.8 ± 13.9	0.0809

Data are presented as mean ± SD values or numbers (and percentages) of the patients. PAF: paroxysmal atrial fibrillation, PerAF: persistent atrial fibrillation, LAD: left atrial diameter, LAV: left atrial volume, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, LVEF: left ventricular ejection fraction.

^a obtained via transesophageal echocardiography.

Table 2
LA and PV voltages of the patients with PAF and PerAF.

	PAF (n=23)	PerAF (n=13)	p Value
LA body	2.50 ± 1.66 mV	1.58 ± 1.35 mV	< 0.0001
LA septum	2.06 ± 1.48 mV	1.03 ± 1.07 mV	0.0232
LA roof	2.50 ± 1.59 mV	1.61 ± 0.92 mV	0.0461
LA anterior wall	2.56 ± 1.99 mV	1.42 ± 1.38 mV	0.0815
LA posterior wall	3.44 ± 1.50 mV	2.10 ± 1.66 mV	0.0071
LA floor	2.18 ± 1.44 mV	1.91 ± 1.49 mV	0.1830
LAA	3.44 ± 2.04 mV	2.76 ± 1.80 mV	0.1654
RSPV antrum	1.81 ± 1.46 mV	1.00 ± 0.64 mV	0.0083
RSPV	1.19 ± 0.72 mV	0.64 ± 0.43 mV	0.0170
RPV carina	1.98 ± 1.07 mV	1.00 ± 0.64 mV	0.0044
RIPV antrum	1.91 ± 1.36 mV	1.23 ± 1.09 mV	0.0330
RIPV	0.92 ± 1.11 mV	0.57 ± 0.46 mV	0.2752
LSPV antrum	1.69 ± 1.04 mV	1.62 ± 1.32 mV	0.8054
LSPV	0.96 ± 0.48 mV	0.74 ± 0.67 mV	0.2807
LPV carina	1.90 ± 1.00 mV	1.33 ± 1.05 mV	0.1404
LIPV antrum	1.73 ± 1.06 mV	1.50 ± 1.66 mV	0.5050
LIPV	1.11 ± 1.01 mV	0.92 ± 0.89 mV	0.6024

Data are presented as mean ± SD values.

PAF: paroxysmal atrial fibrillation, PerAF: persistent atrial fibrillation, LA: left atrial, LAA: left atrial appendage, RSPV: right superior pulmonary vein, RPV: right pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LPV: left pulmonary vein, LIPV: left inferior pulmonary vein.

3.2. LA/PV voltages in the PAF group and PerAF group

The LA and PV bipolar voltages per study group are shown in Table 2. The total LA body, LA septum, LA roof, and LA posterior wall voltages were significantly lower in the PerAF group than in the PAF group. The RSPV, RSPV antrum, RPV carina, and RIPV antrum voltages were also significantly lower in the PerAF group than in the PAF group. However, there was no significant between-group difference in the left PV carina, left PV antrum, and LSPV or LIPV antrum voltages. The distribution of the LA and PV segments with a significant voltage reduction is shown on the 3D geometry in Fig. 2. The LA and PV bipolar voltages in a patient with PAF are shown in Fig. 3, and those in a patient with PerAF are shown in

Fig. 4. The total low-voltage area in patients with PerAF was considerably greater than that in patients with PAF.

4. Discussion

4.1. Main findings

The main study findings can be summarized as follows: The bipolar voltages in the right PVs (RSPV and RIPV), RPV antrum, LA roof, and LA posterior wall were shown to be higher in association with PAF than in association with PerAF. The bipolar voltages in the left PVs (LSPV and LIPV), LPV antrum, LA floor, and LA appendage did not differ significantly between PAF and PerAF.

4.2. Previous studies

Wijffels et al. concluded that “AF begets AF” because they found that a reduction in the atrial refractory period resulting from repeated induction of AF allowed the AF to sustain itself; however, they also reported that this change was completely reversible within 1 week of SR [2]. However, according to Todd et al., sequential 4-week periods of AF resulted in a progressive increase in AF stability independent of the baseline atrial refractory period, which suggested the presence of a second factor in the self-perpetuation of AF with a time course comparable to that of AF-induced ultrastructural changes in the atria [8]. In a dog model of congestive heart failure, Cha et al. showed complete recovery of ionic remodeling after burst-pacing-induced AF but persistence of the AF substrate and structural remodeling [9]. Similarly, Stiles et al. reported that patients with lone PAF, remote from arrhythmia, had bi-atrial abnormalities characterized by structural changes, conduction abnormalities, and sinus node dysfunctions and suggested that these alterations contribute to the “second factor” that predisposes to the development and progression of AF [10]. Recently, EHRA/HRA/APHR/SOLAECE experts proposed the concept of “atrial cardiomyopathies” for the pathogenesis of AF [11].

4.3. Regional differences in LA structural remodeling

In a study conducted by Chang et al., the regional distribution of scars in the left atrium was shown to differ between patients with PAF and PerAF; scarring was frequently observed in the low anteroseptum or at the right PV antrum junction in both patients with PAF and PerAF. However, scarring in the LA lateral isthmus, anterior roof, and posterior roof was more prevalent in patients with PerAF than in those with PAF [12]. According to Marcus et al., the number of low-voltage areas increased in the LA septum and LA posterior wall in patients with AF [13], while according to Stiles et al., the LA posterior wall and LA roof are likely to harbor low-voltage areas in patients with PAF [10]. Teh et al. reported a stepwise reduction in the total mean LA voltage from control to PAF to PerAF and that the percentage of low voltage in the left atrium was the greatest in the posterior wall, septum, roof, and floor [14]. Lin et al. reported that the regional distribution and prevalence of low-voltage zones in the LA differ among PAF, PerAF, and longstanding AF, with the low-voltage zones being the most prevalent in patients with longstanding rhythms, especially in the anterior wall, posterior wall, and roof [5]. Yagishita et al. showed that structural remodeling starts in the PV antra and progresses to other LA regions [15]. In the present study, we showed that the voltages in the LA septum, LA roof, LA posterior wall, RSPV, RSPV antrum, RPV carina, and RIPV antrum were significantly lower in association with PerAF than in association with PAF. The reasons for the selected sites to monitor the initial progression of structural remodeling might be as follows: 1) higher contact force by

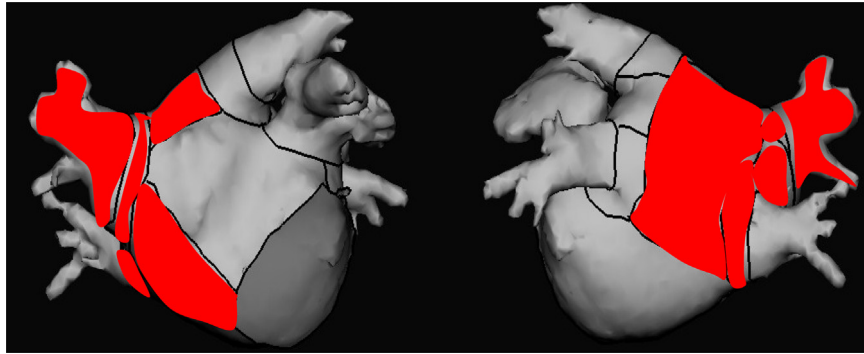


Fig. 2. Left atrial regions in which the bipolar voltage is significantly reduced in patients with persistent atrial fibrillation. Regions of significantly reduced low voltage are indicated in red.

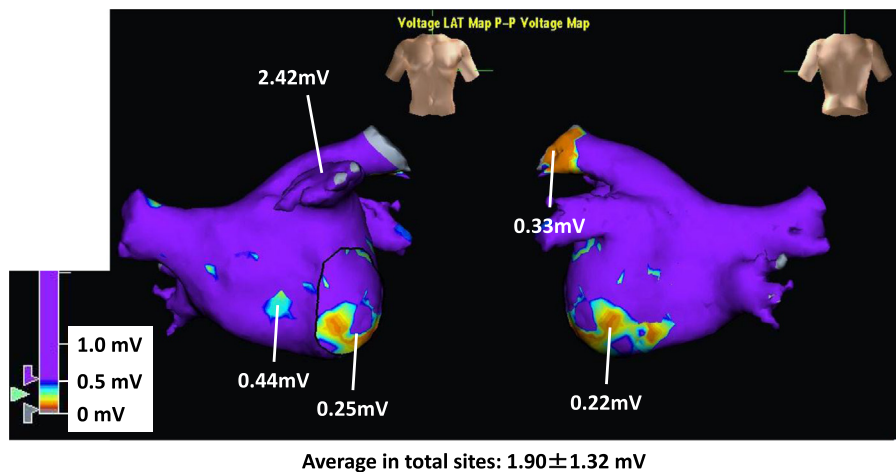


Fig. 3. Voltage map representative of the patients with paroxysmal atrial fibrillation. Note that the low-voltage areas are located at the right superior pulmonary vein and left atrial septum, and the average left atrial voltage is 1.90 ± 1.32 mV.

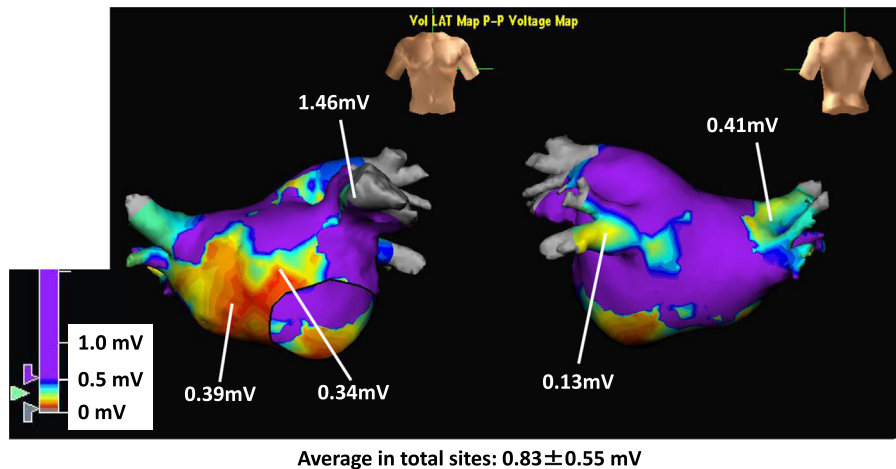


Fig. 4. Voltage map representative of the patients with persistent atrial fibrillation. Note that the low-voltage areas are located at the right superior and inferior pulmonary veins, right inferior pulmonary vein antrum, and left atrial septum, anterior wall, and floor, and the average left atrial voltage is 0.83 ± 0.55 mV.

external structures, such as the ascending aorta, descending aorta, and vertebra, and 2) higher LA wall stress in those areas [16–19]. Therefore, we suggest that LA structural remodeling progresses from the LA roof, posterior wall, and septum and right PVs and their antra associated with the progressive dilation of the LA.

4.4. Limitations

Our study data must be interpreted cautiously in light of the study limitations. The number of our study patients, particularly in

the PerAF group, was small because of the inability to maintain SR before ablation; thus, the statistical differences should be interpreted accordingly. In addition, our study did not include control patients, i.e., patients without a history of AF. Therefore, we could not compare the regional differences in the voltage with the normal value. Further, the patients with PerAF underwent direct current cardioversion 15 min before the electroanatomic mapping, and it is possible that the delivery of the electrical current affected the electrophysiological properties of the atria. We did not compare the data with the normal LA voltage in patients without AF

and the percentage low-voltage area in each segment between PAF and Per AF. Finally, some electrophysiological variables, such as intra-atrial conduction time and ERP, were not assessed in the study. The development of clinical AF is complex and depends not only on the substrate but also on triggers and perpetuators that were not addressed in the study.

5. Conclusions

Regional voltage differences in the LA and PVs appear to differ between patients with PAF and patients with PerAF. The LA structural remodeling characterizing PAF may progress to that characterizing PerAF by expansion from the right PVs and their antra and LA septum, roof, and posterior wall.

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Conflict of interest

The authors declare no conflict of interest related to this study.

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