Original Article

Influence of the Direction of Conduction on the Dominant Frequency of Left Atrial Electrocardiograms During Sinus Rhythm in Patients with Atrial Fibrillation

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Background: Complex electrocardiogram morphologies (atrial fibrillation [AF] nests) in sinus rhythm (SR) recorded by frequency domain techniques can serve as a pathologic substrate for atrial fibrillation (AF). We sought to characterize any direction-dependent and rate-dependent changes in dominant frequency (DF) and high DF sites in the left atrium (LA) in patients with AF.

Methods: Eight patients with AF were included in the study. A basket catheter with 64 electrodes was placed in the LA. Forty-eight bipolar electrocardiograms were recorded during SR and during pacing from the high right atrium (HRA), proximal coronary sinus (CS), and distal CS at various pacing rates, ranging from 600 ms to 250 ms. The frequency domain measures of LA bipolar electrocardiograms were compared during SR and HRA, proximal CS, and distal CS.

Results: The DF was found to be higher during proximal CS and distal CS pacing than during SR. The percentage of high DF (>70 Hz) sites was higher during distal CS pacing than during SR. The various pacing rates applied during HRA, proximal CS, and distal CS pacing did not affect the DF values.

Conclusion: DF of atrial electrocardiograms obtained during SR was influenced by the direction of conduction but not by the pacing rate.

Key words: atrial fibrillation, sinus rhythm, dominant frequency, atrial pacing

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Introduction

Pulmonary vein (PV) isolation (PVI) is a well-established treatment method for paroxysmal atrial fibrillation (PAF)¹⁾. However, the success rate in patients with persistent AF (PerAF) has been suboptimal²⁾. PVI plus ablation of left atrial (LA) complex fractionated atrial electrogram (CFAE) sites by time domain analysis or PVI plus LA high dominant frequency sites (DF) by frequency domain analysis has been shown to result in improved acute and long-term success rates in patients with PerAF^{3,4)}. Fractionated electrograms have also been recorded from the LA during sinus rhythm (SR) in patients with AF⁵⁾. Pachon M et al.⁶⁾ showed that the atrial substrate can be characterized by the frequency spectra obtained from a single electrogram recorded during SR. The authors used frequency spectra to identify “fibrillar” myocardium or “AF nests,” and ablation of such sites has been effective in terms of long-term arrhythmia control in both PAF and PerAF patients⁷⁾. We showed previously that most CFAE sites and high DF sites identified during AF did not correspond to the high DF

sites identified during SR⁸⁾. Therefore, we investigated the effects of the direction and rate of activation on DF and high DF sites found during SR.

Material and Methods

1. Study patients

The study group comprised 8 consecutive patients (7 men, 1 woman; mean age: 59.8 ± 11.5 years) scheduled for their first catheter ablation of AF. Three had paroxysmal AF (PAF: AF lasting less than 7 days), and 5 had persistent AF (PerAF: AF lasting 7 days or more). No patient with cardiomyopathy, valvular heart disease, or congenital heart disease was included in the study. Adequate oral anticoagulation therapy was given for at least 1 month before the ablation procedure, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. Upon admission, transesophageal and transthoracic echocardiography were performed, and baseline echocardiographic data were obtained: LA dimension, maximum LA volume by the prolate ellipsoid method, and left ventricular (LV) ejection fraction by the Teichholz method. The study protocol

was approved by the Institutional Review Board of Nihon University Itabashi Hospital (December 7, 2012, RK-121109-5), and all patients provided written informed consent for their participation.

2. Electrophysiologic study

Electrophysiologic study was performed in all patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl, as described previously^{8,9}. After vascular access was obtained, 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 LA via transseptal puncture, the 3D geometry of the LA and the pulmonary veins (PVs) was reconstructed with the use of an EnSite NavX Classic system (St. Jude Medical, Inc.) and a 64-pole basket catheter (Constellation, EP Technologies/Boston Scientific Corporation, San Jose, CA, USA), which consisted of 8 splines (A–H), each with 8 electrodes 4-mm in length. The basket catheter was deployed in the LA, and the distal end was placed at the left PV antrum (Fig. 1). A basket catheter of adequate size (38 mm with inter-electrode spacing of 3 mm, 48 mm with inter-electrode spacing of 4 mm, or 60 mm with inter-electrode spacing of 5 mm) was chosen for consistent contact with the LA endocardium. We recorded multiple bipolar signals (filter setting: 30–300 Hz, respectively) simultaneously during sinus rhythm (SR). A duo-decapolar catheter (BeeAT, Japan Lifeline Co., Tokyo, Japan) was placed in the coronary sinus (CS) through the right internal jugular vein.

If the patient was in AF, SR electrograms were recorded after internal atrial cardioversion by biphasic energy of 15–20 J. If the patients had immediate recurrence of AF requiring additional cardioversion, the patients were excluded from the analysis. The study was performed after waiting time more than 30 minutes after internal cardioversion.

3. Bipolar signal recordings

Because of the limit on the number of electrodes that can be recorded by the EnSite NavX Classic system (St. Jude Medical, Inc.), signals from 1 proximal electrode of each spline of the basket catheter could not be recorded. Thus, electrograms were recorded from 6 of the 7 bipolar electrode pairs along each spline for a total of 48 bipolar electrograms (6 pairs $\times$ 8 splines) and entered into the analysis. With the basket catheter sitting in a stable position, baseline bipolar signals were recorded from each of the 48 bipoles and stored in the NavX mapping system. DF were calculated from electrograms

obtained during SR and during pacing from the high right atrium (HRA), proximal CS (CS) and distal CS at pacing rates of 600, 500, 400, 300, and 250 ms. To ensure reliability of the DF detection, the lowest noise signal was chosen for analysis. Overall, 11.6 ± 10 sites per patient were excluded.

4. Fast Fourier transform (FFT) analysis

For FFT analysis, the DF (highest power frequency) of a single atrial beat was analyzed by means of the DF software installed in the NavX mapping system (sampling rate: 1,200 Hz; resolution: 0.14 Hz; unrectified, with a Hamming window function, 1 sec in duration) as previously reported^{8,10}. DF was defined as the highest peak frequency of the resulting frequency spectrum at each site with a DF >70 Hz (derived from the 5% upper limit values of the acquired 3,234 points⁸) and appearing bright purple on the SR-DF map produced by the NavX system (Fig. 2).

5. Statistical analysis

Continuous variables are expressed as mean $\pm$ SD values. Baseline echocardiographic variables were compared between the PAF and PerAF patients. Mean DFs were compared between values obtained during SR and those obtained in the proximal CS and distal CS. Mean site-specific DFs obtained under the various pacing rates were also compared. Further, comparison was also made between the percentages of high DF sites found during SR and percentages in the HRA, proximal CS, and distal CS when the pacing rate was set to 600 ms. The percentages of site-specific high DF sites identified under different pacing rates were also compared. Differences were analyzed by Mann-Whitney U test or Wilcoxon signed-rank test, as appropriate. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered significant.

Results

1. Patients' baseline echocardiographic characteristics

In comparing baseline echocardiographic characteristics between the PAF patients and PerAF patients, we found that the LA dimension, LA volume, and left ventricular ejection fraction did not differ significantly (LA dimension: 43.4 ± 6.1 mm vs. 46.3 ± 4.7 mm, respectively [$p = 0.456$], LA volume: 55.3 ± 18.4 cm³ vs. 75.4 ± 16.4 cm³, respectively [$p = 0.180$]), left ventricular ejection fraction ($69.1 \pm 5.3\%$ vs. $56.0 \pm 10.3\%$, respectively [$p = 0.101$]). Cycle length in sinus rhythm was 773.0 ± 27.2 ms.

Fig. 1 Position of the basket catheter in the left atrium.

RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; AP view, antero-posterior view.

Fig. 2 Distribution of the dominant frequencies (DFs) of the left atrial electrogram obtained during high right atrial (HRA), proximal coronary sinus (CS prox.), and distal coronary sinus (CS dist.) pacing at a pacing cycle length of 600 ms (*middle panel*), and distribution of DFs at the same sites during HRA, proximal CS, and distal CS pacing (*right panels*). High DF (>70 Hz) areas are shown in purple (*left panel*).

Note that distribution of DF values differed between pacing sites; mean DF was lowest during HRA pacing (greater yellow-colored area); highest during distal CS pacing (greater purple-colored area); and intermediate during proximal CS pacing (greater blue-colored area); and that peak DF values at different pacing cycle lengths were same during HRS, proximal and distal CS pacing.

Table 1 Cycle length, DF value, and percentage of high DF sites during sinus rhythm and at different pacing sites

	Cycle length (ms)	DF (Hz)	<i>p</i> Value	High DF sites (%)	<i>p</i> Value
Sinus rhythm	773 ± 27.2	44.2 ± 2.6		4.7 ± 3.7	
HRA	600	44.3 ± 3.5	0.783 vs. SR	4.9 ± 4.3	0.922 vs. SR
Proximal CS	600	48.1 ± 5.2	0.078 vs. SR 0.1084 vs. HRA	8.9 ± 5.6	0.125 vs. SR 0.100 vs. HRA
Distal CS	600	50.7 ± 6.3	0.017 vs. SR 0.025 vs. HRA 0.383 vs. Proximal CS	14.1 ± 8.3	0.016 vs. SR 0.018 vs. HRA 0.164 vs. Proximal CS

DF, dominant frequency; High DF, >70 Hz; HRA, high right atrium; CS, coronary sinus.

Table 2 Dominant frequencies and high dominant frequency areas per pacing cycle length at the 3 pacing site

Pacing site	Cycle length (ms)	DF value (Hz)	<i>p</i> Value*	High DF (>70 Hz) sites (%)	<i>p</i> Value*
HRA	600	44.3 ± 3.5		4.9 ± 4.3	
	500	45.8 ± 4.4	0.1453	7.8 ± 5.2	0.1890
	400	45.5 ± 3.1	0.1937	7.8 ± 4.5	0.0890
	300	45.1 ± 4.5	0.2078	7.6 ± 6.2	0.0567
	250	45.9 ± 4.4	0.0907	6.3 ± 5.9	0.4263
Proximal CS	600	48.1 ± 5.2		8.9 ± 5.6	
	500	47.7 ± 5.3	0.3749	8.6 ± 7.7	0.4766
	400	47.4 ± 5.5	0.1604	8.1 ± 6.3	0.1705
	300	49.0 ± 5.2	0.6467	12.8 ± 10.8	0.7040
	250	48.6 ± 4.0	0.1726	10.2 ± 5.8	0.2355
Distal CS	600	50.7 ± 6.3		14.1 ± 8.3	
	500	49.7 ± 4.7	0.1352	10.4 ± 6.4	0.0897
	400	48.7 ± 6.3	0.1001	9.1 ± 6.7	0.0691
	300	50.1 ± 5.1	0.2111	9.1 ± 5.6	0.0829
	250	50.5 ± 3.6	0.2568	9.4 ± 4.8	0.1138

HRA, high right atrium; CS, coronary sinus; DF, dominant frequency.

* versus cycle length of 600 ms.

2. Mean DFs and percentages of high DF sites during SR and in the HRA, proximal CS, and distal CS

The mean LA DFs and percentages of high DF sites identified during SR and during pacing during the HRA, proximal CS, and CS pacing at 600 ms are shown in Table 1. The high-DF site was mainly located at posterolateral LA during SR, HRA, proximal CS, and distal CS pacing (Fig. 2). Mean DF during the distal CS pacing were significantly higher than mean DF recorded during SR and during HRA pacing. The percentage of high DF sites during the distal CS pacing was significantly higher than the percentage identified during SR or HRA pacing.

3. Mean DFs and percentages of high DF sites in the HRA, proximal CS, and distal CS identified during pacing at different cycle lengths

Mean DFs and the percentages of high DF sites calculated from recordings obtained from the HRA, proximal CS, and distal CS during pacing at cycle lengths of 500, 400, 300, and 250 ms did not differ significantly from those obtained at 600 ms (Table 2).

Discussion

1. Spectral analysis of the atrial electrograms during sinus rhythm

Lin et al. reported that 81% of patients with PAF required additional LA substrate modification because high DF (>70 Hz) sites were responsible for sustained AF induced after PVI¹⁰. Saghy et al. reported (1) no significant correlation between fractionated electrograms recorded during SR (SR fractionation [SRF]) and CFAE maps, (2) no significant difference in the distribution of SRF regions between patients with AF and those without AF, and (3) overlap between regions of SRF and areas of wave-front collision at a frequency of 75 ± 13%¹¹. We have also shown that in both PAF and PerAF patients, most CFAE and high DF sites identified during SR did not correspond to the high DF sites or low-voltage areas identified during SR⁸.

2. Direction-dependent conduction abnormalities

Markides et al. showed that the LA endocardium has complex but characteristic patterns of activation

during sinus rhythm, pacing, and AF initiation by pulmonary vein ectopy that are determined largely by the functional properties of atrial musculature¹²⁾. Wong et al. also showed that differing wavefront directions caused changes in conduction velocity, biatrial activation time, site-specific conduction delays, and voltage in both lone AF patients and reference patients, and they also showed that these direction-dependent abnormalities were amplified in the lone AF patients compared to those in the reference patients, who exhibited greater slowing of conduction velocities, prolongation of biatrial activation time, increases in the number and length of lines of conduction block, increase in the proportion of fractionated electrograms, and decrease in voltage during distal CS pacing^{13,14)}. Jadidi et al. showed that LA electrogram fractionation did not match between SR and CS pacing at $70 \pm 10\%$ sites, and activation maps in SR and CS pacing showed that wave collision and regional slow conduction caused electrogram fractionation¹⁵⁾.

Our study showed first that the mean DF and percentage of high DF sites in the LA increased more during left-to-right atrial activation than during right-to-left atrial activation. Therefore, the mechanism of increase in DF during distal CS pacing might in part be explained by anisotropic conduction within the LA leading to increases in the number and length of lines of conduction block and increase in the proportion of fractionated electrograms. Our study did not show rate-dependent changes in mean DF and percentage of high DF sites. Wong et al. reported that the number and duration of double potentials or fractionated signals increased with the earliest captured extrastimulus^{13,14)}. In contrast, we did not find differences in the mean DF value or percentage of high DF sites at different pacing cycle lengths. The conflicting study results might be due in part to the difference between closed-coupled extrastimulus and steady-state pacing.

3. Clinical implications

Sustained AF can be induced by burst pacing after PVI in as many as 30–50% of patients with PAF and in more than 70% of patients with PerAF, and additional atrial substrate modification has been reported^{16,17)}. Pachon M et al. proposed radiofrequency ablation of sites with complex and fractionated atrial electrograms identified by frequency analysis and termed “AF nests” for long-term arrhythmia control⁶⁾. However, in the study described herein, we showed that DF values and the percentage of high DF sites are influenced by the direction of conduction. Therefore, additional parameters, such as voltage information may be needed to ablate high DF sites found during SR¹⁸⁾.

4. Study limitations

Our main study limitation was the small sample size; therefore, we did not examine the data obtained from PAF patients and PerAF patients separately. Further, we did not include control patients without AF because of the need for transseptal puncture and placement of a basket catheter in the LA. In addition, we used the NavX system-automated algorithm to define and detect fractionation intervals and DFs. We cannot rule out the possibility that use of a different automated algorithm with a different mapping system or use of a mapping catheter with different inter-electrode spacing would have yielded different results. Our study included patients with PAF and patients with PerAF, all of whom had preserved left ventricular function and for whom cardioversion prior to ablation was feasible. Thus, our findings may not necessarily apply to the broader AF population. Furthermore, as shown in Fig. 1, the currently available basket catheter leaves nearly 50% of the endocardial LA surface unmapped, and many electrodes do not make sufficient contact, therefore, high-density mapping of whole left atrial chamber is needed to clarify the relation of the direction of conduction on the wavefront collision sites and the high dominant frequency distribution of left atrium^{12,19)}.

Conclusion

Spectral analysis of atrial electrograms during SR was influenced by the direction of conduction but not by the pacing rates. These findings suggest that, with respect to the maintenance of AF, the pathophysiologic role of high DF sites identified in the LA during sinus rhythm needs further evaluation.

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Conflict of interest

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

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