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ORIGINAL ARTICLE

The impact of left atrial pressure on filtered P-wave duration in patients with atrial fibrillation

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Abstract The cause of prolonged filtered P-wave duration (FPD) remains unclear in atrial fibrillation (AF) patients with normal left atrial size. We investigated whether FPD is associated with left atrial pressure (LAP) in AF patients without prominent LA enlargement. This study included 80 patients (48 men, age 65 ± 9 years, 25 persistent AF) with non-valvular AF who underwent catheter ablation (CA) for AF. LAP was measured in sinus rhythm during CA and signal-averaged electrocardiogram was recorded after CA. We retrospectively assessed the clinical and echocardiographic variables. Prolonged FPD was defined as FPD > 120 ms. Prolonged FPD (FPD > 120 ms) was detected in 23/80 patients (29 %). According to univariate analysis, higher mean LAP (14.9 ± 4.4 vs. 10.8 ± 3.5 mmHg, $p < 0.0001$), higher prevalence of persistent arrhythmia, higher BNP, larger LAD, higher E wave, and lower LVEF were associated with Prolonged FPD. According to multivariate analysis, higher mean LAP was the only factor associated with Prolonged FPD ($p = 0.0058$, OR 1.256 for each 1 mmHg increase in mean LAP, 95 % CI 1.068–1.476). Moreover, a significant correlation was observed between FPD and mean LAP ($r = 0.503$, $p < 0.0001$). Prolonged FPD is associated with high LAP in AF patients without prominent left atrial enlargement. Pressure overload of the left atria might cause slowing of atrial electrical activation.

Keywords Filtered P-wave duration · Left atrial pressure · Atrial fibrillation

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with cardiogenic stroke. Catheter ablation (CA) is an effective therapeutic option for AF patients. Because the validity of the CA of AF has become widely recognized, its indications have recently been extended and new techniques have been used in CA [1, 2]. Signal-averaged electrocardiogram (SAECG) is a noninvasive examination that can be extended to the P-wave to provide a more accurate evaluation of atrial conduction. Several studies have reported that filtered P-wave duration (FPD) can detect patients at risk for paroxysmal AF [3] and can serve as a predictive marker of AF recurrence after CA [4]. Previous studies reported that FPD was useful in identifying patients at risk for paroxysmal AF and was significantly correlated with the inter- and intra-atrial conduction delays or wide spreading of atrial activation [3]. This electrical abnormality is generally associated with left atrial (LA) enlargement [5] or mechanical atrial dysfunction [6]. However, the cause of prolonged FPD remains unclear in AF patients with normal left atrial size. We hypothesized that LA function, such as left atrial pressure (LAP), is associated with an electrical abnormality in patients without anatomical abnormalities and investigated whether FDP is associated with the functional abnormality in AF patients without prominent LA enlargement.

Materials and methods

Patient population

This study included 104 patients with non-valvular AF who underwent CA for AF in the Hyogo College of Medicine between June 2013 and December 2014. All patients

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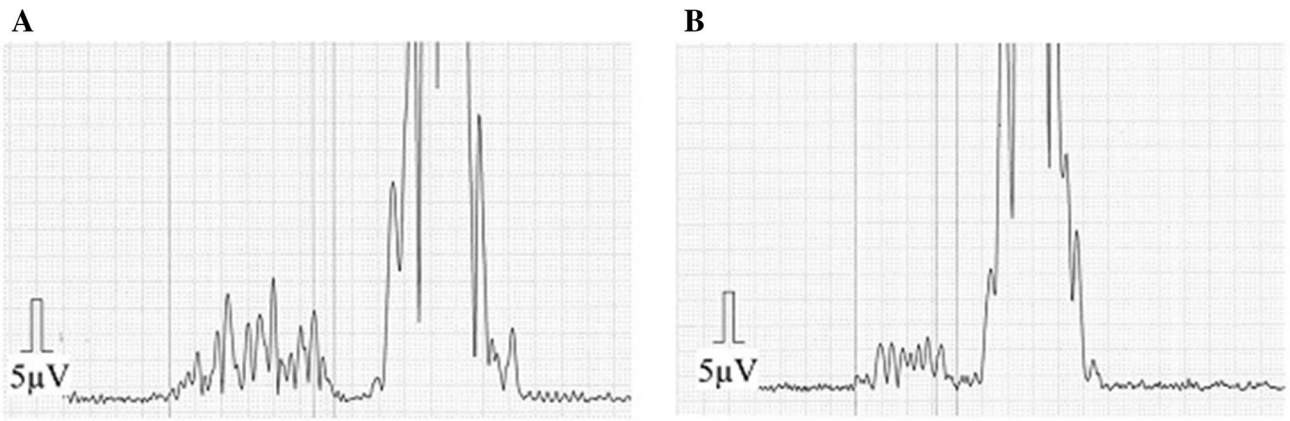

Fig. 1 Example of signal-averaged P-wave electrocardiogram recordings and measurement of filtered P-wave duration (FPD) after catheter ablation: **a** FPD: 150 ms, mean left atrial pressure (LAP): 20 mmHg (**b**) FPD: 84 ms, mean LAP: 8 mmHg

provided written informed consent before CA and were >18 years old. Patients with prior heart surgery (two patients), permanent pacemakers (three patients), huge LA (>50 mm) (four patient), and patients requiring dialysis (five patients) were excluded. Fourteen patients who were taking amiodarone within 3 months of evaluation were excluded (a patient with prior heart surgery was taking amiodarone, and a patient had huge LA). The remaining 80 patients (48 men, age 65 ± 9 years, 25 persistent AF) were registered in this study. Anti-arrhythmic drugs (AADs), except for amiodarone, were discontinued at least five half-lives before CA.

A paroxysmal arrhythmia was defined as recurrent AF that terminated spontaneously within 7 days, and a persistent arrhythmia was defined as recurrent AF that persisted beyond 7 days or that lasted less than 7 days but necessitated pharmacological or electrical cardioversion [7]. Ethics approval of the present study was obtained from the local review committee.

P-wave signal-averaged electrocardiography

P-SAECG was recorded in the first day after CA in all patients using a Cardio Star FCP-7541 (Fukuda Denshi, Tokyo, Japan). The software uses a P-wave trigger and provides filtering and automatic delineation of the averaged P-wave. Automatic measurements include total filtered and unfiltered P-wave duration. Electrocardiographic data are obtained in the *X*, *Y*, *Z* planes, and the three leads are combined into a vector magnitude VM ($VM = \sqrt{(X^2 + Y^2 + Z^2)}$). Qualified P-waves are correlated with a P-wave template, and only P-waves with a correlation coefficient >0.95 are taken into account for the averaging process for filtering (bidirectional Butterworth high-pass filter of 40 Hz) and for analysis. The endpoint for the averaging process is predetermined (200 beats), and only recordings with a residual noise level <0.4 μV are used. Two independent observers who were blinded to the clinical data verified all automatic measurements. The incorrect beginning point or the end point of the P-wave was modified according to visual delineation (Fig. 1). If their measurements were different, they were averaged. Prolonged FPD was defined as FPD > 120 ms [3].

Echocardiographic imaging

Transthoracic echocardiography (TTE) was also performed on all patients within 1 week before the CA procedure using a Prosound F75 (Hitachi Aloka Medical, Tokyo, Japan) with a 3.88-MHz transducer probe. All patients were measured for the left atrial diameter (LAD), E wave, E/e' ratio, left ventricular diameter during end diastole (LVDd), and left ventricular ejection fraction (LVEF). Left ventricular hypertrophy (LVH) was defined as a posterior wall or interventricular septal thickness >12 mm. If this thickness was <12 mm, the LV mass index was calculated. If the LV mass index was greater than 95 (female) or 115 (male), the patient was considered to have LVH.

Catheter ablation procedure

The right femoral vein was used for the insertion of catheters. In the absence of a patent foramen ovale, a transseptal puncture was performed using the Brockenbrough technique. We used the bispectral index (BIS) monitor (Vista A-2000, Nihon Kohden, Tokyo, Japan) as an indicator of sedative effect. All patients were sedated with intravenous dexmedetomidine to maintain BIS at 50–70.

All patients underwent circumferential pulmonary vein isolation (PVI) guided by electroanatomical mapping combined with image integration. The circumferential ablation lines were created under the guidance of a 3-D mapping

system (CARTO XP System; Biosense Webster, CA, USA or EnSite Velocity System; St. Jude Medical, MN, USA). Segmental radiofrequency (RF) application was performed with a 3.5-mm externally irrigated-tip quadripolar ablation catheter (Navistar Thermocool SF; Biosense Webster). The endpoint was the establishment of the bidirectional conduction block between the LA and the PV. In patients with non-PV foci initiating the AF, additional procedures were performed to eliminate them. If AF was converted to an atrial tachycardia (AT), it was mapped and ablated using a three-dimensional (3-D) mapping system. We targeted the ablation of any ATs induced by programmed stimulation with isoproterenol. Cavotricuspid isthmus (CTI) ablation was performed after the PVI in 69 patients (86 %) with the endpoint of bidirectional conduction block.

Left atrial pressure

Arterial pressure (AP) and LAP were measured after transseptal puncture under deep sedation. The AP and LAP were measured in sinus rhythm (SR) through the sheath that was connected to a pressure transducer and were recorded with a hemodynamic monitoring system. AF was induced by atrial high rate pacing in patients with sinus rhythm. Those pressures were measured after AF lasted 2 min or more. Five consecutive heartbeats were valued at the end of expiration in the AF rhythm. The internal cardioversion was performed using a 6-Fr 8 + 4 + 8 polar catheter (BeeAT, Japan Lifeline, Tokyo, Japan) placed into the coronary sinus and along the lateral wall of the right atrium via the right jugular vein. The cardioversion protocol was started at 5 J and was increased incrementally in 5-J steps (to a maximum of 30 J) until successful CV. After sinus conversion, five consecutive heartbeats were measured at the end of expiration in steady SR. The maximum LAP (LAP_{max}) was defined as the maximum height of the v wave, and the minimum LAP (LAP_{min}) was defined as the minimum of the *x* trough. The mean LAP was defined as [LAP_{min} + 1/3(LAP_{max} − LAP_{min})] at the average of five heartbeats. In the same way, the systolic AP (SAP), diastolic AP (DAP), and mean AP (MAP) were measured in SR.

Statistical analysis

All data are expressed as the mean value ± standard deviation. Statistical comparisons were made by a Student's *t* test. Differences between categorical variables were evaluated with a Chi-square analysis. A p value <0.05 was considered to indicate statistical significance. Univariate analyses were performed using Student's *t* test or Chi-square analysis. The variables that were found to be significant in univariate analysis were entered into a multivariate analysis. The independent association with a prolonged FPD was evaluated using a multivariate analysis. All analyses were performed with StatView version 5.0 software (SAS Institute, Cary, NC, USA).

Results

Patient population

All 80 patients underwent successful cardioversion to SR. The LAP in 80 patients could be measured in stable SR, and were registered in this study. The baseline characteristics of the patients are described in Table 1. Of the 80 patients who were registered in this study, the mean age was 65 ± 9 years; 48 patients (60 %) were male, and 25 patients had persistent AF.

Prolonged FPD (FPD > 120 ms) was detected in 23 patients (29 %). When compared with the Normal FPD (FPD ≤ 120 ms) group, there was a higher prevalence of persistent arrhythmia in the Prolonged FPD group. When compared with patients with Normal FPD, the patients with Prolonged FPD showed higher BNP. The other characteristics did not differ between the Normal FPD and Prolonged FPD groups (Table 1).

Baseline medication use, including use of beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, statin, and anticoagulants, did not differ between the Prolonged FPD and Normal FPD groups.

Echocardiographic characteristics

The echocardiographic characteristics are described in Table 2. When compared with the patients with Normal FPD, the patients with Prolonged FPD showed larger LAD, higher E wave, and lower LVEF. The E/e' ratio, LVDd, and the prevalence of LVH did not differ between the Normal FPD and Prolonged FPD groups.

Ablation procedure and pressure characteristics

The ablation characteristics are described in Table 3. All patients had successful CPVI (first session: 66 patients [83 %]). Sixty-nine patients (86 %) underwent CTI ablation, and 32 patients (40 %) underwent additional procedures (superior vena cava isolation: 18 patients, box isolation: 9 patients, mitral isthmus ablation: 2 patients, AT ablation: 6 patients, or ganglionated plexi ablation: 6 patients). There were no patients who underwent complex fractionated atrial electrogram ablation. All patients were in SR at the end of the procedure. None of procedural characteristics differed between the Normal FPD and Prolonged FPD groups.

Table 1 Baseline characteristics

	Prolonged FPD ($n = 23$)	Normal FPD ($n = 57$)	p value
Male gender, n (%)	17 (74)	31 (54)	0.1066
Age[a]	68 ± 9	65 ± 9	0.1845
Body height (m)[a]	1.67 ± 0.09	1.63 ± 0.09	0.1497
Body weight (kg)[a]	65 ± 11	63 ± 12	0.4823
BMI (kg/m^2)[a]	23.4 ± 3.1	23.4 ± 3.3	0.9214
HT, n (%)	13 (57)	29 (51)	0.6473
DM, n (%)	4 (17)	11 (19)	0.8432
SHD, n (%)	7 (30)	11 (19)	0.2803
Prior CHF, n (%)	3 (13)	5 (9)	0.5643
Persistent arrhythmia, n (%)	14 (61)	11 (19)	0.0003
BNP (pg/ml)[a]	131 ± 133	72 ± 82	0.0178
HANP (pg/ml)[a]	76 ± 54	67 ± 145	0.7769
Creatinine (mg/dl)[a]	0.8 ± 0.3	0.7 ± 0.0.2	0.0937
HbA1c (NGSP) (%)[a]	6.2 ± 1.1	6.0 ± 0.7	0.2206

BMI Body Mass Index, *HT* hypertension, *DM* diabetes mellitus, *TIA* transient ischemic attack, *SHD* structural heart disease, *CHF* congestive heart failure, *TIA* transient ischemic attack, *AF* atrial fibrillation, *BNP* brain natriuretic peptide, *HANP* human atrial natriuretic peptide, *NGSP* national glycohemoglobin standardization program

[a] Mean ± SD

Table 2 Echocardiographic characteristics

	Prolonged FPD ($n = 23$)	Normal FPD ($n = 57$)	p value
LAD (mm)[a]	42 ± 5	39 ± 6	0.0452
E wave (cm/s)[a]	78 ± 18	69 ± 17	0.0452
E/e'[a] ratio	10 ± 3	10 ± 3	0.7822
LVDd (mm)[a]	48 ± 4	48 ± 3	0.9806
LVH, n (%)	1 (4)	4 (7)	0.6553
LVEF (%) *	61 ± 10	67 ± 9	0.0113

LAD left atrial diameter, *LVDd* left ventricular diameter during end diastole, *LVH* left ventricular hypertrophy, *LVEF* left ventricular ejection fraction

[a] Mean ± SD

The pressure characteristics are described in Table 3. When compared with the patients with Normal FPD, the patients with Prolonged FPD showed higher mean LAP. Heart rate at SAECG and mean AP did not differ between the Normal FPD and Prolonged FPD groups.

Univariate and multivariate analyses

Multivariate analyses are described in Table 4. According to univariate analysis, mean LAP, persistent arrhythmia, BNP, LAD, E wave, and LVEF were associated with Prolonged FPD. According to multivariate analysis, higher mean LAP ($p = 0.0058$, OR 1.256 for each 1 mmHg increase in mean LAP, 95 % CI 1.068–1.476) was the only factor associated with Prolonged FPD. Moreover, a significant correlation was observed between FPD and mean LAP (Fig. 2, $r = 0.503$, $p < 0.0001$) (Fig. 2).

Discussion

Main findings

The objective of this study was to investigate the influence of LAP on FPD. In multivariate analysis, higher mean LAP was the only independent factor related to Prolonged FPD in our study. To the best of our knowledge, this is the first study illustrating that higher LAP influences FPD. The higher LAP could be what causes Prolonged FPD. On the other hand, left atrial size was not associated with FPD. Faggiano et al. tried to determine the influence of LAP [Pulmonary capillary wedge pressure (PCWP) measured by right-sided heart catheterization] and LAD (measured by echocardiography) to FPD in patients with congestive heart failure [8]. They found that FPD was more dependent on the level of PCWP than on the LAD. This finding is consistent with results from the present study. Our results confirmed that higher LAP might play a role in prolonging FPD.

Influence of left atrial pressure on filtered P-wave duration

Previous studies have reported that FPD is useful to predict which patients have a high risk of AF recurrence after CA

Table 3 Procedural and pressure characteristics

	Prolonged FPD ($n = 23$)	Normal FPD ($n = 57$)	p value
Procedural time (min)[a]	160 ± 31	174 ± 45	0.1954
RF energy (J)[a]	53,227 ± 20,624	53,158 ± 20,077	0.9891
RF time (min)[a]	35 ± 13	35 ± 12	0.9831
1st session, n (%)	18 (78)	48 (84)	0.5262
PVI, *n* (%)	23 (100)	57 (100)	N.S.
CTI ablation, *n* (%)	20 (87)	49 (86)	0.9072
Additional procedure, *n* (%)	10 (43)	22 (39)	0.6867
HR at SAECG (bpm)[a]	71 ± 12	76 ± 11	0.0712
FPD (ms)[a]	139 ± 17	106 ± 11	<0.0001
Mean AP (mmHg)[a]	86 ± 12	83 ± 20	0.5207
Mean LAP (mmHg)[a]	14.9 ± 4.4	10.8 ± 3.5	<0.0001

RF radio frequency, *PVI* pulmonary vein isolation, *N.S.* not significant, *CTI* cavotricuspid isthmus, *HR* heart rate, *SAECG* signal-averaged electrocardiography, *FPD* filtered P-wave duration, *AP* artery pressure, *LAP* left atrial pressure

[a] Mean ± SD

Table 4 Variables associated with prolonged FPD

	Univariate analysis	Multivariate analysis	
	p value	p value	OR (95 % CI)
Mean LAP	<0.0001	0.0058	1.256[a] (1.068–1.476)
Persistent arrhythmia	0.0003	0.0600	3.406 (0.949–12.220)
BNP	0.0178	0.9705	1.000 (0.993–1.007)
LAD	0.0452	0.4664	1.044 (0.929–1.174)
E wave	0.0452	0.4340	1.015 (0.978–1.053)
LVEF	0.0113	0.3912	0.970 (0.906–1.039)

OR odds ratio, *CI* confidence interval, *LAP* left atrial pressure, *BNP* brain natriuretic peptide, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction

[a] For each 1 mmHg increase in mean LAP

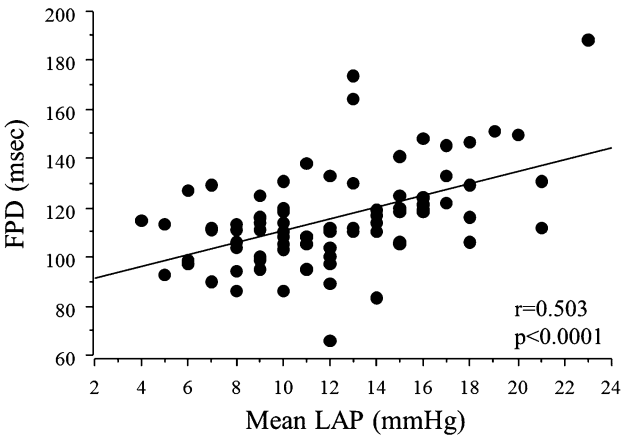

Fig. 2 A significant correlation was observed between filtered P-wave duration (FPD) and mean left atrial pressure (LAP) ($r = 0.503$, $p < 0.0001$)

[4]. However, the mechanisms of Prolonged FPD remain unclear. In previous studies, various factors, such as LAD, PCWP [8], autonomic tone [9], sex [10], age [11], and certain drugs [12] have been shown to influence FPD.

In our study, LAP was an independent factor related to Prolonged FPD. We assessed several potential mechanisms of Prolonged FPD in patients with high LAP. First, high LAP may decrease biatrial conduction time. Previous studies reported that FPD was useful in identifying patients at risk for paroxysmal AF and was significantly correlated with inter- and intra-atrial conduction delays [3]. Another study reported an association between P-wave duration and atrial electromechanical delay, as assessed by tissue Doppler echocardiography [13]. They concluded that the P-wave duration is significantly correlated with the atrial electromechanical delay. The electrical abnormality is caused by atrial stretching due to AF in early phase, and structural alterations, such as fibrosis and left atrial enlargement is caused after the early phase [5]. John et al. studied the effects of the reversal of chronic stretching on the electrophysiological characteristics of atria in humans [14]. In their study, after the reversal of chronic stretching, there was an acute and marked reduction in LA pressure with increased conduction velocity in both atria. Therefore, it is possible that high LAP has an effect on FPD. Second, high LAP may cause an increased dispersion of effective refractory periods (ERPs). Previous studies in an animal model suggested that an increase in atrial pressure causes an increased dispersion of ERPs, which slows conduction velocity and increases AF inducibility [15]. However, human data are limited, and further investigation is necessary. Third, high LAP may cause delayed activation of the PV muscle sleeve. Date et al. studied the contribution of

PV cardiac muscles to the P-wave using standard vectorcardiography and electrocardiography recorded before and after CA [16]. They found that the morphology of the P-wave changed after PVI, and that the myocardial sleeves of the PV played an important role in the formation of the P-wave. Okumura et al. reported that the latest atrial activation site was located within the PVs in most cases [17]. They also suggested that the atrial late potential is derived from delayed activation of the muscle sleeves within the PVs. Shortening of FPD after PV isolation was reported to be a predictor of successful AF ablation [18, 19]. Therefore, delayed activation of PV muscle sleeves due to high LAP may be a cause of prolonged FPD. Our results could not be explained by this mechanism because we used FPD after PVI.

Clinical implications

Our findings indicate that FPD indices obtained from SAECG are noninvasive and easy-to-apply predictors for high LAP. FPD may be a useful marker of LA dysfunction and probably reflects the extent of the atrial disease and remodeling. Moreover, we hope to investigate the effect of drug-induced reduction of LAP on FPD. In the future, FPD might be an indicator of the therapeutic efficacy of various drugs, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Study limitations

There were several limitations to our study. First, this was a retrospective study with a small number of patients in a single center. Therefore, further prospective study with a larger number of patients is necessary. Second, we could not assess the potential of the PV muscle sleeve because FPD was measured after CA in all patients. Shortening of FPD after PV isolation was reported to be a predictor of successful AF ablation [18, 19]. We had to measure FPD before CA; however, this could not be performed in 25 patients with persistent arrhythmia. Third, the measurement methods of FPD were different among prior studies [3, 4]. Holmqvist et al. compared different measuring methods and showed that different aspects of the methodology, such as the noise level, had profound effects on the estimation of FPD [20]. Therefore, we used the most standard definition. Fourth, the CA procedure might affect FPD. However, there were no differences in the proportion of the patients who underwent the additional procedures between prolonged FPD group and normal-FDP group. Therefore, the procedure characteristics might have a small effect on FPD in this study. Finally, AAD, such as amiodarone, may have influenced FPD. However, the patients who were taking amiodarone within 3 months of evaluation were excluded from this study. Therefore, AAD might have a very small effect on FPD in this study.

Conclusions

Prolonged FPD is associated with high LAP in AF patients without prominent left atrial enlargement. Pressure overload of the left atria might cause slowing of atrial electrical activation.

Compliance with ethical standards

Funding No funding was received for the study.

Conflict of interest There are no conflicts of interest on the part of the author.

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