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ORIGINAL ARTICLE

Atrial fibrillatory wave amplitude revisited: A predictor of recurrence after catheter ablation independent of the degree of left atrial structural remodeling

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Abstract

Background: *The fibrillatory wave amplitude (FWA) during atrial fibrillation (AF) is thought to reflect structural atrial remodeling, but it remains unclear what determines the FWA.*

Methods: *One hundred and fourteen consecutive patients were prospectively studied who underwent catheter ablation of AF. The mean FWA was computed by automated surface electrocardiography analyses. The extent of the left atrial (LA) voltage-defined atrial fibrosis and conduction properties were estimated by a three-dimensional high-density electroanatomical mapping system. The LA size was evaluated by transthoracic echocardiography. The study patients were divided into two groups according to an FWA in lead V1 above the median value of 46 µV (high FWA group, n = 57) or below 46 µV (low FWA group, n = 57).*

Results: *There were no differences in the age, gender,* CHA_2DS_2*-VASc score, prevalence of paroxysmal AF, medications, ablation strategy, and LA volume index between the two groups. The LA low voltage areas in the low FWA group were not different from those in the high FWA group. The total LA activation time and local LA conduction velocity did not differ between the two groups. During a median follow-up of 710 days, the recurrence rate after ablation was significantly higher in patients with a low FWA than a high FWA (log-rank* $p = 0.02$*). In a multivariate analysis, non-paroxysmal AF, the LA volume index, and FWA were independent predictors of recurrence after ablation.*

Conclusions: *The FWA was not correlated with the markers of atrial structural remodeling. Nevertheless, the FWA could still provide information for predicting the clinical outcome after AF ablation.* (Cardiol J 2023; 30, 6: 974–983)

Key words: atrial fibrillation, electrocardiogram, ablation, fibrillatory wave, remodeling

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of an ischemic stroke, heart failure, and death [1]. Recently, catheter ablation of AF has become a more common treatment option because catheter ablation is more effective for maintaining sinus rhythm than antiarrhythmic drugs [2]. Yet, the recurrence rate of AF after ablation remains high in patients with advanced atrial structural remodeling (i.e., chamber enlargement and development of fibrosis) [3–5].

The atrial fibrillatory wave amplitude (FWA) on the surface electrocardiogram (ECG) is known to gradually decrease in the natural time course of

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persistent AF [6], which may reflect the progressive nature of AF with electrical and structural atrial remodeling. It has been reported that patients with a lower FWA were associated with a larger left atrial (LA) size [7] and increased recurrence rate after ablation of persistent AF [8]. Although the FWA was measured manually in those old studies, Lankveld et al. [9] employed a more sophisticated method to compute the complexity of the fibrillatory waves, where several time-domain and frequency-domain parameters were measured. They concluded that the FWA was the best predictor of the long-term outcome of catheter ablation in persistent AF patients. However, it remains poorly understood what determines the FWA.

Conflicting results were reported regarding the relationship between the FWA and LA size [7, 10, 11]. Intracardiac bipolar voltage maps have been used to estimate structural remodeling in which the low-voltage areas (LVA) are considered a marker for the presence of atrial fibrosis. Intuitively, a greater LVA burden would be expected in patients with a lower FWA. However, a recent study showed that the FWA was not associated with the LVA extent in long-standing persistent AF patients [12].

To address this issue, the present study further examined the relationships among the FWA, LVA in high-density intracardiac LA voltage maps, conduction velocities in the LA, echocardiographic variables, and clinical outcome of catheter ablation in paroxysmal and non-paroxysmal AF patients.

Methods

One hundred and fourteen consecutive patients referred to our hospital for their index catheter ablation of AF were prospectively enrolled. This study was approved by the Institutional Review Board and Ethical Committee of the Nippon Medical School Musashi-Kosugi Hospital. As stated in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines for the management of patients with AF, non-paroxysmal AF was defined as continuous AF lasting longer than 7 days [13].

All patients underwent transthoracic echocardiography before the ablation procedure. The LA diameter, LA volume, left ventricular diameter, and left ventricular ejection fraction were assessed. The LA volume was measured by the biplane area-length method, and the LA volume index was defined as the ratio of the LA volume to the body surface area.

Surface ECG analysis

Surface ECGs were digitally recorded with a 500-Hz sampling for a 10 s frequency using an FCP-7541 (Fukuda Denshi., Ltd., Tokyo Japan). The ECG signals synchronized with the R-wave were averaged. Each QRST complex of the R-wave signal-averaged ECG was subtracted at the position where the square error of the difference was the smallest. The gap between the offset and onset after each subtraction was linearly interpolated. The frequency analysis of the subtracted waveform (F-wave) was performed by a fast Fourier transform (FFT, with a frequency resolution: 0.24 Hz). The FFT analysis window for 512 sample point intervals was shifted and repeated 6 times. The amplitude (μV) at the maximum peak frequency is the square root of the power value of the FFT. The amplitude of the FFT result represents the change in the amplitude at each frequency of the time domain waveform. The FWA was calculated as the mean of the amplitude of each FFT result. Patients were divided into two groups according to the FWA in lead V1: patients with an FWA above the median value of 46 μV (high FWA group) or below 46 μV (low FWA group).

Electrophysiological study and catheter ablation

All procedures were performed under deep sedation using a three-dimensional electroanatomical mapping CARTO®3 system (Biosense Webster, California. USA). Intravenous unfractionated heparin was administered after a successful transseptal puncture, targeting an activated clotting time of 300–350 s. Before ablation, a color-coded bipolar voltage map of the LA was constructed using a 5-splined high-density mapping catheter (PentaRay®, Bisosense Webster) during pacing from the coronary sinus in the setting of sinus rhythm. Thus, internal cardioversion (BeeAT; Japan Lifeline, Tokyo, Japan) was performed if AF was present at the beginning of the procedure. The acquisition of the LA voltage map was abandoned if electrical cardioversion was required more than 3 times for immediately reinitiating AF. The bipolar electrograms were filtered by a bandpass to frequencies between 16 and 500 Hz. Criteria for an adequate LA geometry were > 1,500 points (mean number of points: 2,553 ± 1,009) that were homogeneously distributed to create the entire LA chamber. The LVA was defined as a surface area with a bipolar peak-to-peak electrogram amplitude < 0.5 mV, as reported previously [3]. The LA was divided into five regions (1: anterior including the LA appendage, 2: posterior, 3: inferior, 4: septum, and 5: roof) to study the regional differences in the LVA.

All patients underwent circumferential pulmonary vein (PV) isolation. Contiguous lesions by a point-by-point radiofrequency (RF) application were created at the level of the LA antrum encircling the ipsilateral right and left PVs using an open-irrigated contact-force sensing catheter (ThermoCool SmartTouch®SF, Biosense Webster) targeting an ablation index (CARTO®3, Biosense Webster) of 500 for the anterior wall and 400–450 for the posterior wall. RF power was set at 50 W throughout the procedure, with an irrigation flow of 15 mL/min using power control mode. A steerable sheath (Agilis, St. Jude. Medical, Inc., Minnesota, USA) was used for the ablation catheter in all procedures. In patients with a long superior vena cava (SVC) sleeve (> 30 mm) or in whom ectopic beats originating from the SVC triggered AF, an electrical isolation of the SVC was also made [14]. Isolation of the LA posterior wall was performed at the operators' discretion.

Further, the electrical activation time of the whole LA was measured, which was defined as the conduction time from the pacing site to the latest activation site in the LA (total LA activation time), and the local conduction velocity of the posterior LA (local LA conduction velocity).

Clinical follow-up

All patients were seen for follow-up every 2 to 3 months, or sooner if they experienced symptoms suggesting arrhythmia recurrence. Twelve-lead ECGs were obtained at each hospital visit, and 24-hour Holter monitoring was performed when necessary. Freedom from recurrence was defined as the absence from atrial tachyarrhythmias (AF, atrial flutter, and atrial tachycardia) lasting more than 30 s beyond a 3-month blanking period.

Statistical analysis

Continuous variables are expressed as the median (interquartile range) or mean ± standard deviation, as appropriate. Differences between the continuous values were assessed using an unpaired two-tailed t-test for normally distributed continuous variables, the Wilcoxon rank-sum test for skewed variables, and χ^2 test (with the Fisher exact test) for nominal variables. The relationship between two variables was examined with the Pearson correlation test. The time to recurrence was estimated using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazards model analysis (univariate and multivariate) was performed to determine which variables were significantly related to the recurrence of atrial tachyarrhythmias. All analyses were performed using R 4.0.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). A $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

The patient characteristics at baseline are summarized in Table 1. There were no differences in the age, gender, prevalence of paroxysmal AF, comorbidities, and CHA_2DS_2-VASc score between the high and low FWA groups. Patients with a low FWA had higher body weights and body surface area than those with a high FWA. The echocardiographic findings including the LA volume index, laboratory findings, and medications were comparable between the two groups.

Relationship between the FWA and degree of LA remodeling

High-density LA voltage maps that fulfilled the adequate geometry criteria were obtained before ablation in 47 patients. The median LVA of the whole LA in the high FWA group did not differ from that in the low FWA group (13.0 [8.1–18.9] vs. 11.1 [8.0–17.8] cm^2, $p = 0.88$). Examples of the LA voltage map exhibiting a high FWA despite a higher LVA and low FWA despite a lower LVA are shown in the case of paroxysmal AF (Fig. 1) and non-paroxysmal AF (Fig. 2). There was no correlation between the FWA and LVA in the whole LA. Even when each subdivided LA region was examined, no correlation between the FWA and LVA was identified (Fig. 3).

Because no differences in the LA structural remodeling between the high and low FWA patients were identified, the conduction properties of the LA by the total LA activation time and local LA conduction velocity were evaluated (Fig. 4). Neither of them significantly differed between the patients with a high and low FWA.

Catheter ablation and clinical follow-up

Sixty-nine (61%) patients underwent a PV isolation only. Additional ablation including an SVC isolation, LA posterior wall isolation, and both was performed in 13 (11%), 21 (18%), and 11 (10%) patients, respectively. The proportion of each ablation strategy did not statistically differ between the high and low FWA groups ($p = 0.16$).

Table 1. Study patient characteristics.

	Overall (n = 114)	High FWA (n = 57)	Low FWA (n = 57)	P
Age [years]	68 ± 12	69 ± 12	66 ± 12	0.11
Sex (male/female)	81/33	44/13	37/20	0.15
Body weight [kg]	67 ± 13	64 ± 11	70 ± 13	< 0.01
Body surface area [m^2]	1.73 ± 0.19	1.69 ± 0.19	1.78 ± 0.19	0.02
Paroxysmal AF	72 (63%)	40 (71%)	32 (56%)	0.12
Comorbidities				
Hypertension	76 (67%)	37 (65%)	39 (69%)	0.69
Diabetes mellitus	27 (24%)	14 (25%)	13 (23%)	0.83
CHA_2DS_2-VASc score	2.40 ± 1.46	2.40 ± 1.43	2.40 ± 1.51	1.00
Echocardiographic findings				
LVEF [%]	61 ± 14	62 ± 16	61 ± 13	0.73
LVDd/LVDs [mm]	50 ± 8/34 ± 9	50 ± 9/33 ± 11	50 ± 7/34 ± 7	0.96/0.98
LAVI [mL/m^2]	43 ± 17	43 ± 15	43 ± 19	0.87
Laboratory findings				
eGFR [mL/min/1.73 m^2]	60.6 ± 18.4	60.0 ± 18.0	61.6 ± 18.9	0.56
NT-proBNP [pg/mL]	642 [277–1530]	920 [346–1733]	476 [161–1116]	0.06
Medications				
ACEI/ARB	51 (45%)	27 (47%)	24 (42%)	0.57
Beta-blockers	71 (62%)	40 (70%)	31 (54%)	0.08
Class I antiarrhythmic drugs	31 (27%)	17 (30%)	14 (25%)	0.53
Amiodarone	7 (6%)	5 (9%)	2 (4%)	0.24

AF — atrial fibrillation; LVEF — left ventricular ejection fraction; LVDd — left ventricular end-diastolic dimension; LVDs — left ventricular end-systolic dimension; LAVI — left atrial volume index; eGFR — estimated glomerular filtration rate; NT-proBNP — N-terminal pro-B-type natriuretic peptide; ACEI/ARB — angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers

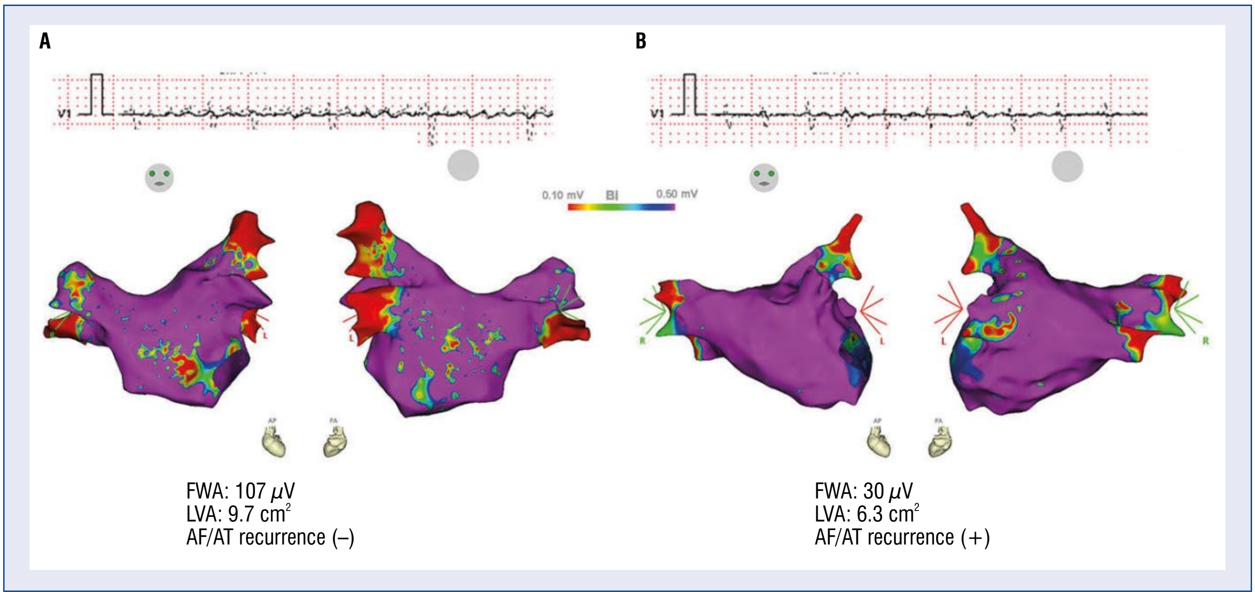

Figure 1. Lack of a correlation between the atrial fibrillatory wave amplitude (FWA) and low-voltage area (LVA) in paroxysmal atrial fibrillation (AF) patients. A low FWA would be expected to have a larger LVA. Examples of QRST--subtracted atrial electrocardiograms and electroanatomical voltage maps, which did not follow that expectation are shown. The high FWA patient (**A**) had a larger LVA than the low FWA patient (**B**). The low FWA patient had an AF/atrial tachyarrhythmia (AT) recurrence during the follow-up but the high FWA patient did not.

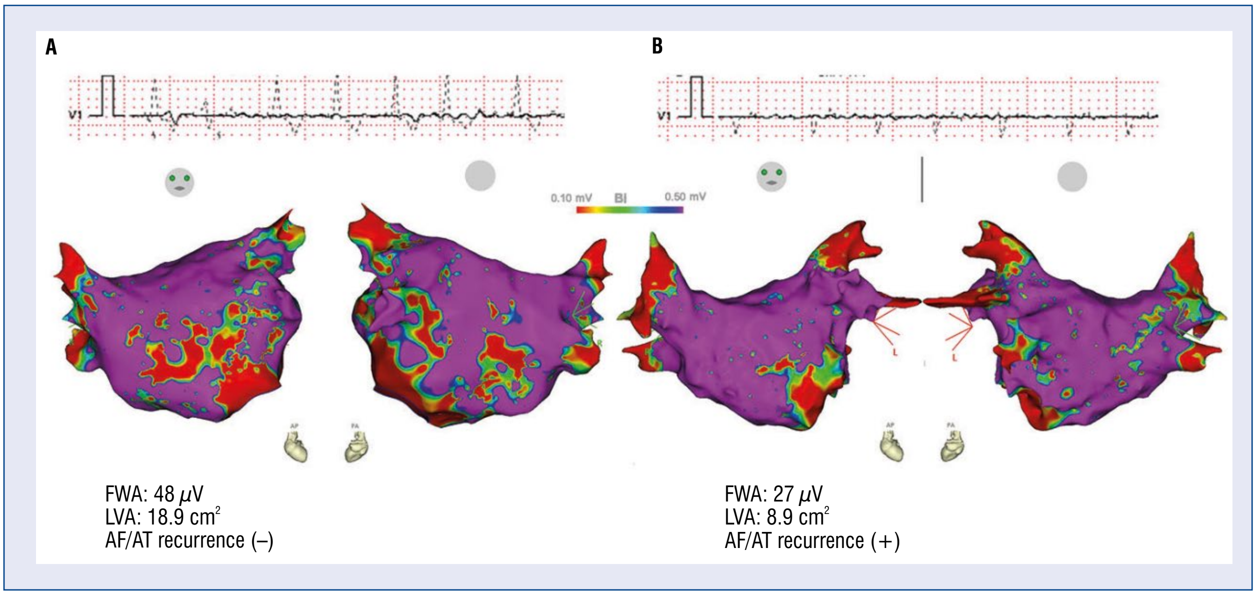

Figure 2. Lack of a correlation between the fibrillatory wave amplitude (FWA) and low-voltage area (LVA) in non--paroxysmal atrial fibrillation (AF) patients. In these examples, the high FWA patient (**A**) had a larger LVA than the low FWA patient (**B**), similarly to paroxysmal AF patients as shown in Figure 1. The low FWA patient had recurrence, but the high FWA patient did not.

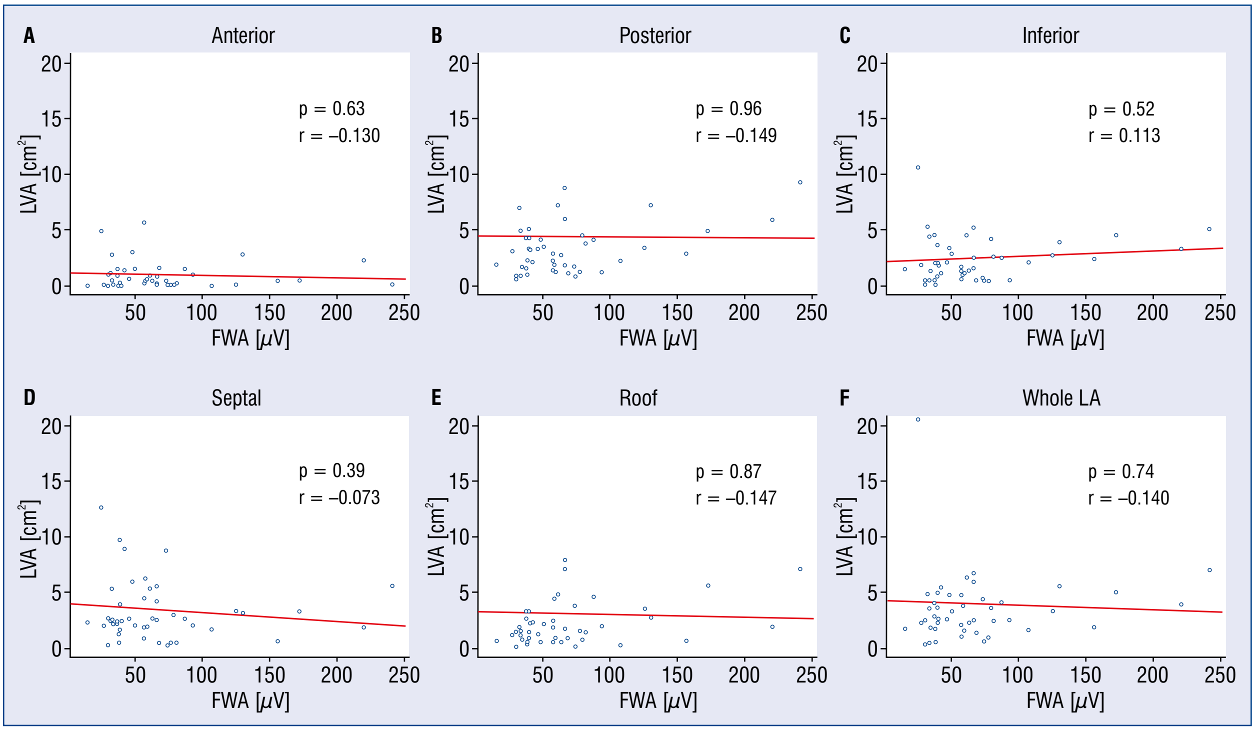

Figure 3. Relationship between the fibrillatory wave amplitude (FWA) and low-voltage area (LVA) in the subdivided left atrial (LA) regions (**A.** Anterior; **B.** Posterior; **C.** Inferior; **D.** Septal; **E.** Roof) and whole LA (**F**). No significant correlation between the FWA and LVA was noted in the whole LA or any subdivided LA region.

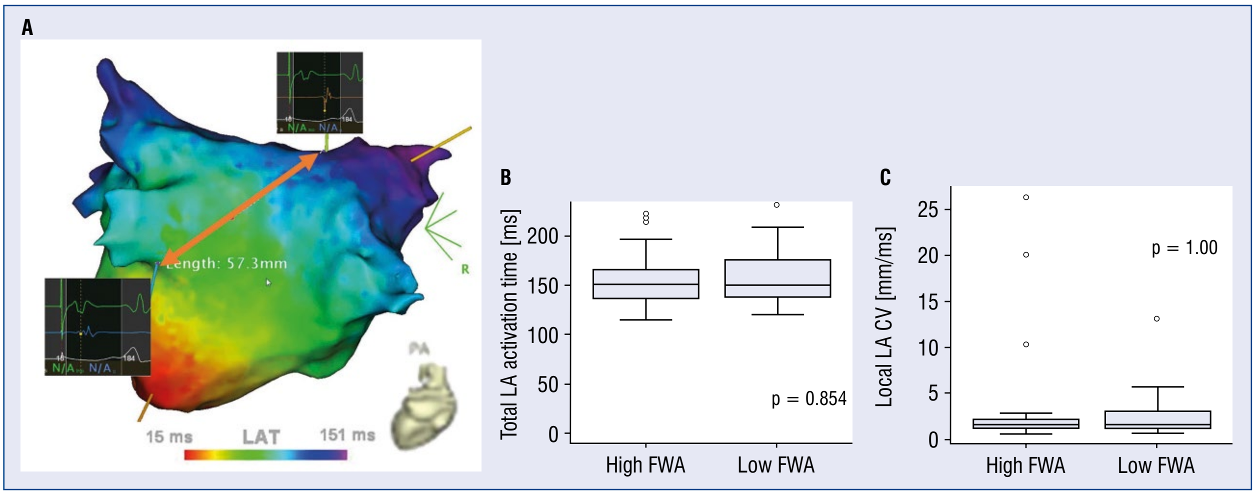

Figure 4. Total left atrial (LA) activation time and local LA conduction velocity (CV). **A.** The local LA CV was calculated by dividing the distance from the inferior ostium of the left inferior pulmonary vein (PV) to the superior ostium of the right superior PV (arrow) by the conduction time between these two sites. The total LA activation time (**B**) and local LA CV (**C**) did not differ between the high and low FWA groups; PA — postero-anterior view; LAT — local activation time.

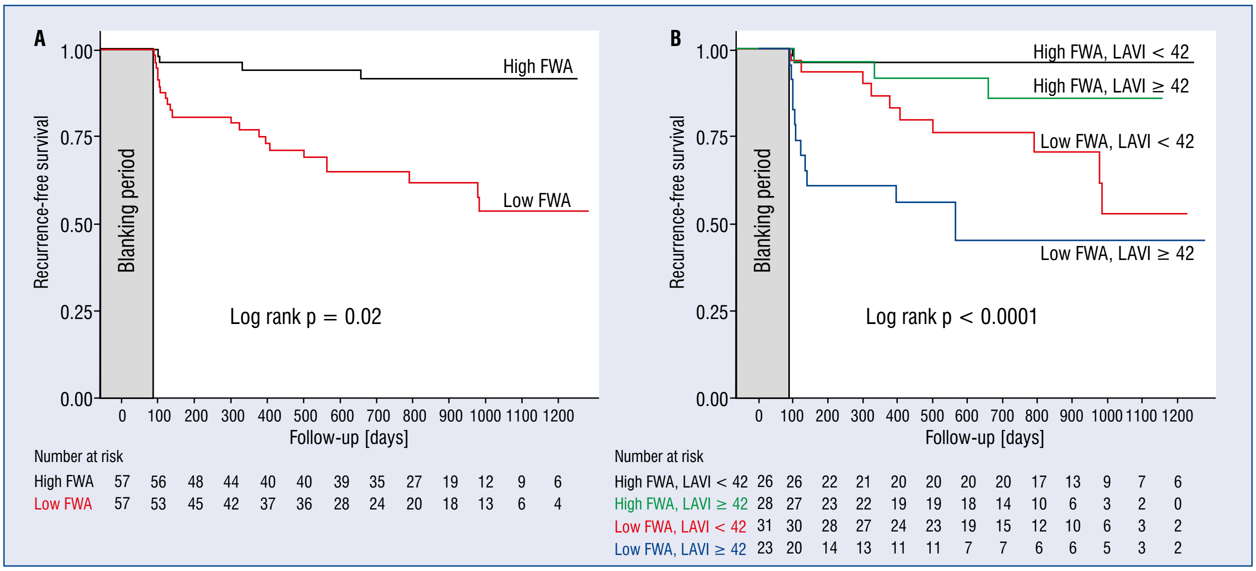

Figure 5. Kaplan-Meier survival curves showing the freedom from atrial tachyarrhythmias after a single ablation procedure stratified by the fibrillatory wave amplitude (FWA) (**A**) and combination of the FWA and left atrial size (**B**); LAVI — left atrial volume index.

The median follow-up period after discharge was 710 [301–971] days. The recurrence-free survival rate after a single procedure was 77% (93% and 61% in the high and low FWA groups, respectively) in the entire population. The recurrence rate was significantly higher in patients with a low FWA than high FWA (log-rank p = 0.02) (Fig. 5A). The recurrence rate was substantially higher in patients with an LA volume index greater than 42 mL/m^2 (hazard ratio 2.60 [95% confidence interval 1.25–5.40], p = 0.01). Then, the effect of the FWA according to the LA size on recurrence after AF ablation was estimated (Fig. 5B). Even when the LA size was considered, the patients with a low FWA had a higher recurrence rate than the patients with a high FWA. In both groups, an LA volume index greater than 42 mL/m^2 was associated with higher recurrences. Figure 6 shows the

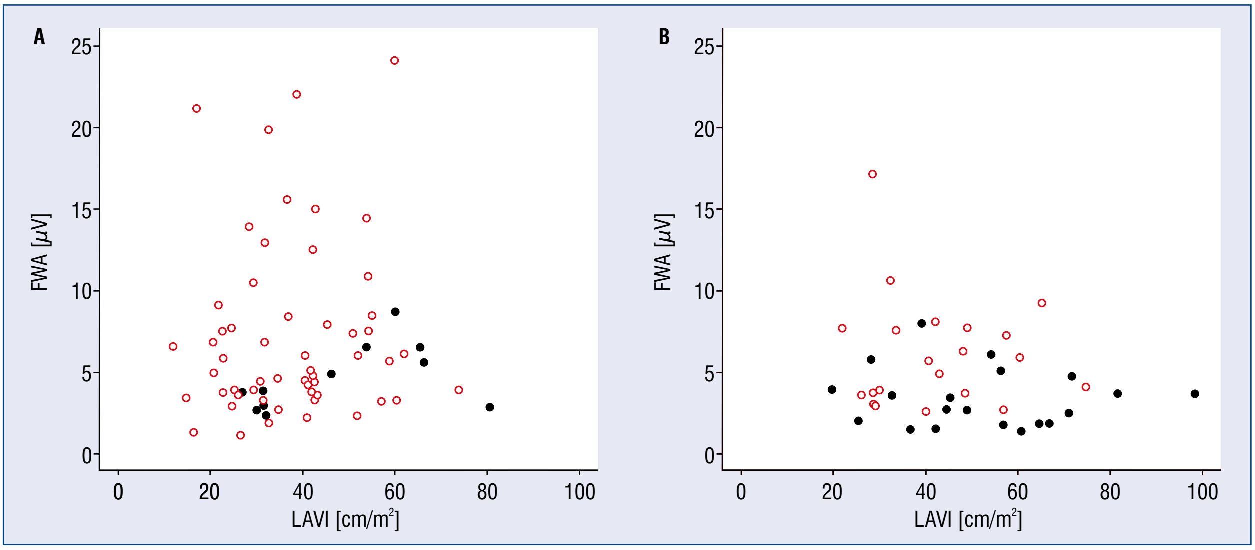

Figure 6. Relationship between the fibrillatory wave amplitude and left atrial volume index (LAVI) in paroxysmal atrial fibrillation (AF) (**A**) and non-paroxysmal AF (**B**) patients. The closed black dots represent patients with recurrent atrial tachyarrhythmias after catheter ablation; FWA — fibrillatory wave amplitude.

relationships among the FWA, LA volume index, and recurrence after ablation according to the AF type. There was no correlation between the FWA and LA volume index in patients with paroxysmal AF ($r = 0.04$, $p = 0.75$) and non-paroxysmal AF ($r = -0.21$, $p = 0.17$). Regardless of the type of AF, the patients with recurrent atrial tachyarrhythmias (black dots) had lower FWAs over the wide range of LA volume index values.

Because these study patients were not homogenous in terms of the ablation strategy, the recurrence was also estimated for each ablation strategy (**Suppl. Fig. S1**). In the PV isolation only group (n = 69), the recurrence rate was significantly lower in patients with a high FWA than low FWA. In patients who underwent additional ablation, the difference in the recurrence rate did not reach a significant level probably because of the relatively small number of patients in each group. However, a lower tendency to recur was observed in patients with a high FWA who underwent a PV isolation + LA posterior wall isolation or PV isolation + LA posterior wall isolation + SVC isolation.

Among 31 (27%) patients who developed recurrence of atrial tachyarrhythmias after the index RF ablation, 17 had a second ablation session. Among 17 patients, PV re-connections were responsible for recurrence in all 6 high FWA patients. On the other hand, 8 of 11 low FWA patients (73%) had recurrences that were attributable to non-PV foci ($p < 0.01$).

In a univariate analysis, the body weight, non-paroxysmal AF, LA volume index, and FWA were significantly associated with recurrence of atrial tachyarrhythmias after AF ablation. In a multivariate analysis, the body weight no longer predicted atrial tachyarrhythmia recurrence, while non-paroxysmal AF, the LA volume index, and FWA remained significant predictors of atrial tachyarrhythmia recurrence after AF ablation (Table 2).

Discussion

Prior studies have investigated the relationship between the FWA and ablation outcome in patients with non-paroxysmal AF [8, 9], while the present study also included paroxysmal AF and showed that a low FWA predicted recurrence after AF ablation irrespective of the AF type. Also, the ablation outcome has been reported to be associated with the degree of atrial structural remodeling represented by the LA size and/or atrial fibrosis detected by the LVA in the electroanatomical voltage map [4, 5] or delayed enhancement cardiac magnetic resonance imaging [3]. If the extent of the atrial fibrosis negatively corresponded with the FWA, a poor ablation outcome in low FWA patients could have been readily understood. However, the current study revealed no relationship among the FWA, LA size, and LVA, which agreed with the recent study by Kiedrowicz et al. [12]. Thus, according to available research, this is the first study

Table 2. Predictors of recurrence of atrial tachyarrhythmias after radiofrequency catheter ablation.

	Univariate analysis		P	Multivariate analysis		P
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Age (years)	0.995	0.967–1.025	0.76			
Male	0.527	0.258–1.077	0.08			
Body weight [kg]	1.034	1.011–1.058	< 0.01	1.013	0.991–1.045	0.26
Body surface area [m^2]	5.95	0.942–37.59	0.06			
CHA_2DS_2-VASc score	1.059	0.750–1.500	0.75			
Antiarrhythmic agents	0.644	0.277–1.50	0.31			
Low voltage area [cm^2]	1.02	0.999–1.041	0.06			
Non-paroxysmal AF	4.144	1.987–8.643	< 0.01	2.534	1.154–5.563	< 0.01
LAVI [mL/m^2]	1.038	1.018–1.059	< 0.01	1.025	1.005–1.046	0.016
FWA [μV]	0.970	0.953–0.998	< 0.01	0.975	0.955–0.993	< 0.01

AF — atrial fibrillation; CI — confidence interval; LAVI — left atrial volume index; FWA — atrial fibrillatory wave amplitude

to have demonstrated that the FWA was a predictor of recurrence after AF ablation independent of the degree of atrial enlargement and fibrosis.

The contributing factors to the FWA should include: (1) the atrial mass associated with hypertrophy and/or chamber enlargement; (2) atrial fibrosis and degeneration of atrial myocytes; (3) the degree of complexity of the fibrillatory wave dynamics. The AF etiology also affects the FWA. The FWA was positively related to the LA size in rheumatic heart diseases but negatively related to the LA size in non-rheumatic heart diseases, possibly because atrial hypertrophy is more prominent in rheumatic heart diseases [10, 15]. Because the atrial size gradually increases in the natural course of persistent AF [16], it is plausible that very long-lasting non-rheumatic AF patients would have a lower FWA due to the advancement of structural LA remodeling. In our study, 63% of the patients had paroxysmal AF and the degree of LA remodeling was moderate (mean LA volume index: 43 mL/m^2). This may explain why the LA size was similar between the high and low FWA groups in the present cohort. Further, the relationship between the FWA and voltage-defined LA fibrosis burden could not be identified. Thus, the mechanism of a low FWA was not attributable to the LA structural remodeling in this study.

Not only the atrial structural remodeling but the complexity of the fibrillatory wave dynamics should determine the FWA. When patients have more organized wavelet excitation in the atria, the simultaneously activated atrial mass becomes larger, resulting in larger vectors in a certain direction. Larger electrical vectors are expected to produce a high FWA. On the other hand, a low FWA could be caused by an increase in the heterogeneity of the atria for some reason (e.g., aging, underlying cardiac diseases, etc.), leading to a higher number of wavebreaks and wavelets with a more non-uniform atrial excitation. Moreover, focal activations arising from the outside of the PVs might contribute to the non-uniform atrial excitation because non-PV foci were responsible for the recurrence of atrial tachyarrhythmia in the majority of low FWA patients in this study. This disorganized atrial activity should result in more cancellation of electrical vectors and hence a lower FWA.

Importantly, a low FWA was an independent predictor of recurrence after ablation, even though the difference in the structural remodeling between the high and low FWA patients was not evident. Thus, the high complexity of the fibrillatory wave dynamics associated with inherent or subclinical electrophysiological abnormalities would be responsible for the low FWA and its poorer ablation outcome in this study.

We employed an automated ECG analysis to measure the FWA. The automated ECG analysis would allow us to measure lower F-waves with higher reproducibility than a manual ECG analysis and might prevent a potential bias introduced by choosing large and easily measurable F-waves. The cut-off level of the FWA by a median value of the present data (46 μV) was lower than the conventional cut-off level of 100 μV used in manually-analyzed studies. Results were in line with the lower FWAs observed in the automatically-analyzed study [9].

Limitations of the study

There were several limitations of the present study. First, this study was conducted in a single center with a relatively small number of patients. Second, the incidence of recurrent atrial tachyarrhythmias should have been underestimated since asymptomatic AF episodes can frequently be overlooked in patients without an implantable cardiac monitoring device. Third, a high-density LA voltage map that fulfilled the qualification criteria was obtained in only 47 (41%) patients mainly because repetitive AF or re-initiating AF after electrical cardioversion discouraged us from completing the high-density voltage map of the entire LA. Nevertheless, the present results were considered valid because the clinical characteristics of the patients with and without high-density mapping did not significantly differ (paroxysmal AF: 68% vs. 60%, $p = 0.36$; low FWA: 40% vs. 57%, $p = 0.09$; LA volume index: 42 ± 16 vs. 43 ± 17 mL/m^2, $p = 0.66$, respectively). Fourth, 62% of the patients had beta-blockers, 27% class I antiarrhythmic drugs, and 6% amiodarone during the study. All those drugs could influence the LVA and conduction velocity. However, there were no statistical differences in the LVA and conduction velocities between patients with and without those medications (**Suppl. Fig. S2**). Moreover, the proportion of patients taking beta-blockers, class I antiarrhythmic drugs, and amiodarone did not statistically differ between the high and low FWA groups. Finally, we performed RF ablation using the high-power (50 W) short-duration setting that has recently been reported to reduce not only the procedure and fluoroscopy time but also the rate of PV re-connections and recurrence of atrial tachyarrhythmias as compared to conventional RF settings [17]. The predictive value of the FWA for clinical outcomes might have somewhat differed if the conventional RF power (20–35 W) had been used.

Conclusions

An automatically-measured FWA did not reflect the degree of atrial structural remodeling in AF patients without severely-remodeled atria. Although it remains unclear what determines the FWA, it predicts clinical outcomes after ablation. The FWA is an old measurement but deserves reappraisal of its clinical utility. The FWA could provide useful information in addition to the established predictors of recurrence after AF ablation.

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Conflict of interest: None declared

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