## Original Article

# Electrical Excitation of the Pulmonary Venous Musculature May Contribute to the Formation of the Last Component of the High Frequency Signal of the P Wave

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Pulmonary veins (PVs) have been shown to play an important role in the induction and perpetuation of focal AF. Fifty-one patients with AF, and 24 patients without AF as control subjects, were enrolled in this study. Signal-averaged P-wave recording was performed, and the filtered P wave duration (FPD), the root-mean-square voltage for the last 20, 30 and 40 ms (RMS20, 30, and 40, respectively) were compared. In 7 patients with AF, these parameters were compared before and after the catheter ablation. The FPD was significantly longer and the RMS20 was smaller in the patients with AF than those without AF. Because RMS30 was widely distributed between 2 and 10 μV, the AF group was sub-divided into two groups; Group 1 was comprised of the patients with an RMS30 $\geq 5.0\,\mu\text{V}$, and group 2, $< 5.0\,\mu\text{V}$. In group 1, short-coupled PACs were more frequently documented on Holter monitoring, and exercise testing more readily induced AF. After successful electrical disconnection between the LA and PVs, each micropotential parameter was significantly attenuated. These results indicate that the high frequency signal amplitude of the last component of the P wave is relatively high in patients with AF triggered by focal repetitive excitations most likely originating from the PVs. That is, attenuation by the LA-PV electrical isolation, and thus the high frequency P signals of the last component, may contain the electrical excitation of the PV musculature.
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### Introduction

Previous studies evaluating the P wave characteristics with signal-averaged electrocardiography (SAECG) showed that filtered P wave duration (FPD) was significantly longer in patients with paroxysmal atrial fibrillation (AF) than in those without,[1–3] and that it might be useful in predicting the transition from paroxysmal to persistent AF. However, the usefulness of variables other than the FPD, associated with the SAECG such as the root-mean-square (RMS) voltage of the last component of the filtered P wave still remains controversial.

Recently, repetitive firing arising from cardiac vascular structures including the pulmonary veins (PVs), superior vena cava and coronary sinus has been shown to be crucial in the development and even perpetuation of paroxysmal AF.[4–6] It has been proven histologically[7–10] that there is cardiac muscle

tissue (musculature) that extends specifically into the pericardial aspect of the PVs, and that musculature has a great deal of fibroid degeneration and a complicated fiber orientation (anisotropy). Therefore, these tissues have been considered to possess an arrhythmogenic potential[10,11] and their electrical excitation might be reflected in the SAECG as a part of the high frequency signals of the P wave. It was also shown that the extension of myocardium was more frequently present in the PVs in the patients with a history of AF than in those without AF.[11] Furthermore, the patients with a history of AF had longer average length of myocardial extension, compared with the patients without AF.[8,11]

Therefore, it is hypothesized that the P wave characteristics might be different between the patients with and without AF. It is also conceivable that P wave variables might differ in patients with paroxysmal AF which is initiated by repetitive excitations mainly from the PVs, as compared with that of AF patients without such a clinical feature.

Consequently, the aim of the present study was to analyze the filtered P wave in detail, and to evaluate the possible contribution of the PV excitations in forming the high frequency signals.

### Methods

Our study population was comprised of 51 patients (40 males and 11 females, mean age $60 \pm 10$ years, range 36–80 years) with symptomatic paroxysmal AF that was clinically documented within the period from October 2000 to December 2003. The patients who had been diagnosed and treated for severe valvular heart disease, coronary artery disease, congestive heart failure, congenital heart disease, chronic obstructive pulmonary disease, other cardiac arrhythmias such as sinus node dysfunction, atrioventricular block, and other supraventricular tachycardias, or those who had undergone open heart surgery were excluded. Those with diabetic neuropathy or thyroid function disturbances were also excluded from this study. All study patients underwent a standard clinical check up including echocardiography, Holter monitoring, Treadmill exercise testing, and P wave triggered signal-averaged electrocardiogram (P-SAECG). A Treadmill exercise test was performed using the standard Bruce protocol. Using the echocardiogram, the area of the left and right atria (LA area, RA area), and left ventricular ejection fraction (LVEF) were estimated from the apical 4-chamber view.

Twenty-four patients without a history of AF and without structural heart disease (16 males and 8 females, mean age $63 \pm 15$ years) served as the control group. Three control patients had chronic hepatitis, 11 had paroxysmal supraventricular ta-

**Table 1** Clinical and study characteristics.

| | AF (n = 51) | Control (n = 24) | p value (AF vs C) | Group 1 (n = 30) | Group 2 (n = 21) | p value (1 vs 2) |
|---|---|---|---|---|---|---|
| Clinical characteristics   Age (years) | $60 \pm 10$ | $63 \pm 15$ | NS | $59 \pm 11$ | $62 \pm 7$ | NS |
| Gender (man) | 40 (78%) | 16 (66%) | <0.01 | 25 (83%) | 15 (71%) | NS |
| Period of illness (years) | $3.9 \pm 2.7$ | — | — | $4.4 \pm 3.3$ | $3.4 \pm 2.2$ | NS |
| continuous time of fibrillation (hours) | $2.6 \pm 1.8$ | — | — | $0.8 \pm 0.2$ | $4.4 \pm 3.3$ | <0.01 |
| Treadmill exercise test performed | 37 (72%) | — | — | 22 (73%) | 15 (71%) | NS |
| PAC induction (cases) | 30 (58%) | — | — | 25 (83%) | 5 (23%) | <0.01 |
| AF induction (cases) | 13 (25%) | — | — | 13 (59%) | 0 (0%) | <0.01 |
| Holter monitoring | | | | | | |
| total number of PACs (beats) | $844 \pm 1355$ | — | — | $1200 \pm 1995$ | $488 \pm 718$ | <0.05 |
| P on T type PACs (beats) | $320 \pm 946$ | — | — | $599 \pm 1675$ | $50 \pm 217$ | <0.01 |
| documented numbed of AF (times) | $3.1 \pm 5.4$ | — | — | $4.8 \pm 10.1$ | $0.4 \pm 0.9$ | <0.01 |
| Echocardiography          LVEF (%) | $67 \pm 7$ | $63 \pm 6$ | NS | $68 \pm 6$ | $67 \pm 8$ | NS |
| LA area (cm$^2$) | $20.4 \pm 3.6$ | $17.9 \pm 1.9$ | NS | $19.7 \pm 2.4$ | $21.1 \pm 4.8$ | NS |
| RA area (cm$^2$) | $15.7 \pm 2.5$ | $16.6 \pm 1.5$ | NS | $15.5 \pm 2.1$ | $16.0 \pm 2.8$ | NS |

Clinical characteristics of patients with AF and control subjects

The data are expressed as the mean value $\pm$ SD. PAC = premature atrial contraction; LVEF = left ventricular ejection fraction; LA = left atrium; RA = right atrium. Group 1: RMS30 $\geq$ 5.0 μV; Group 2: RMS30 < 5.0 μV.

chyarrhythmias which were not associated with manifest WPW syndrome and treated with catheter ablation, 2 had diabetes mellitus, and the remaining 8 did not have significant present illness. These subjects also underwent P-SAECG and echocardiogram (**Table 1**).

### P wave triggered signal-averaged electrocardiogram

Before the P-SAECG recordings were performed, all antiarrhythmic agents including $\beta$-blockers were discontinued for at least five half lives. The P-SAECG was recorded in the awakened supine position during sinus rhythm at a paper speed of 200 mm/sec using a corrected orthogonal lead (Frank XYZ leads) utilizing a MAC5000 (GE Marquette Medical System Inc., Milwaukee, Wisconsin, USA), which was set to the P wave triggered SAECG mode. The patients' skin was cleansed with rubbing alcohol and wiped with gauze, and Ag/AgCl electrodes were attached to the chest. The subjects were covered with a sheet to protect against static electricity during the SAECG recordings. Using a bidirectional band-pass filter with a cut-off frequency of 40 to 250 Hz, filtered P waves were obtained. The recording was stopped immediately after 250 beats when a noise level below $0.3\,\mu V$ was achieved. If the noise level remained above $0.3\,\mu V$ after averaging 250 beats, the recording was continued up to a maximum of less than 450 beats until the peak noise level was reduced below $0.5\,\mu V$. The P wave complexes from three bipolar electrograms were combined into a vector sum, $\sqrt{(X^2 + Y^2 + Z^2)}$. The onset of the P wave was determined as a microvolt value increase above $0.5\,\mu V$ from the isoelectric line. Similarly, the offset was determined as the point the amplitude decreased below $0.5\,\mu V$.

The following P-SAECG variables were analyzed: (1) total filtered vector combined P wave duration (FPD); and (2) root-mean-square voltage for the last 20, 30 and 40 msec of the signal averaged P wave (RMS20, RMS30 and RMS40).

### Electrophysiological study and catheter ablation

In 7 AF patients electrophysiological study confirmed that repetitive firings from pulmonary veins (PV) provoked AF. Radiofrequency catheter ablation was undertaken to isolate electrically the culprit PVs, and then isolated every other PV as far as possible. Eventually, a total of 20 PVs were successfully isolated from the LA at the end of the ablation session (7 left superior PVs, 6 left inferior PVs, 4 right superior PV and 3 right inferior PV).

A 5-Fr decapolar catheter (Spiral SC, St. Jude Medical, St. Paul, Minnesota, USA) was used for circumferential mapping of the left atrium-PV junction, and a 7-Fr ablation catheter (Marinr, Medtronic Co, Minneapolis, Minnesota, USA) for the RF delivery. The RF energy was delivered with a target temperature of $50\,^{\circ}C$ and set to the power-limited temperature control mode (less than 30 watts) using an RF generator (Atakr, Medtronic Co, Minneapolis, Minnesota). After a mean of $8 \pm 5$ RF deliveries (mean ablation time $405 \pm 301$ sec), all targeted PVs were successfully isolated from the LA, and this was confirmed by the elimination of the PV potentials during either sinus rhythm or regular pacing from the coronary sinus. In these 7 patients, the P-SAECG was repeatedly recorded 2 days after

**Table 2**   Comparison of micropotential parameters.

| | Control (n = 24) | AF (n = 50) | p Value (C vs AF) | Group 1 (n = 29) | Group 2 (n = 21) | p Value (1 vs 2) |
|---|---|---|---|---|---|---|
| Acquired averaged beats (beats) | $330 \pm 70$ | $345 \pm 84$ | NS | $320 \pm 75$ | $360 \pm 90$ | NS |
| Noise level ($\mu V$) | $0.3 \pm 0.2$ | $0.3 \pm 0.1$ | NS | $0.4 \pm 0.1$ | $0.3 \pm 0.1$ | NS |
| Micropotential parameters | | | | | | |
| FPD (msec) | $116 \pm 11$ | $133 \pm 12$ | <0.001 | $133 \pm 11$ | $133 \pm 14$ | NS |
| RMS20 ($\mu V$) | $5.1 \pm 1.9$ | $3.0 \pm 1.1$ | <0.001 | $3.2 \pm 1.4$ | $2.7 \pm 0.5$ | NS |
| (range) | | | | (1–7) | (1–4) | |
| RMS30 ($\mu V$) | $6.0 \pm 2.4$ | $5.0 \pm 2.2$ | NS | $6.4 \pm 1.3$ | $3.1 \pm 0.7$ | <0.001 |
| (range) | | | | (5–10) | (2–4) | |
| RMS40 ($\mu V$) | $7.1 \pm 2.7$ | $6.5 \pm 2.7$ | NS | $8.2 \pm 2.2$ | $4.1 \pm 1.1$ | <0.001 |
| (range) | | | | (5–15) | (3–5) | |

Comparison of the micropotential parameters of the P-SAECG in patients with AF and control subjects
The data are presented as mean value $\pm$ SD. FPD = filtered P wave duration; RMS20, RMS30, RMS40 = root-mean-square voltage for the last 20, 30, and 40 msec of the signal-averaged filtered P-waves, respectively.
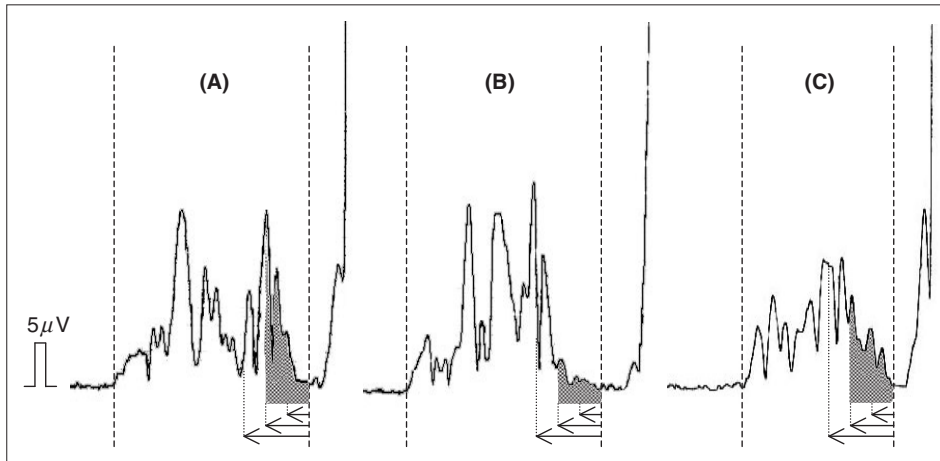
**Figure 1**  Representative records of signal-averaged filtered P waves.
Panel A exhibits P-SAECG data in a patient (group 1: see the result section for explanation) with AF in which the amplitude of the last component of the P wave is relatively high and almost comparable to that of a control subject (panel C). Panel B represents another characteristic P wave in AF patients (group 2), in which the amplitude of the last component of the P wave is smaller than the control. The dotted lines indicate the beginning and terminal portion of the filtered P wave. The arrows are the last 20, 30 and 40 msec from the terminal portion of the P wave, respectively. The gray zone demonstrates the RMS30. A = group 1, B = group 2, C = control subjects
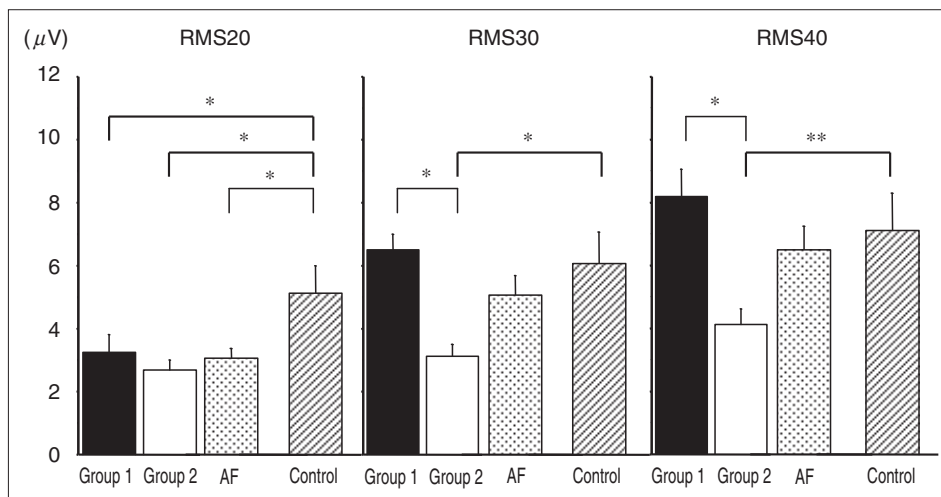


**Figure 2**  A comparison of the root-mean-square voltage for the last 20, 30 and 40 msec (RMS20, 30, and 40, respectively) of the signal-averaged filtered P waves between the AF group (sub-divided into group 1 and group 2) and the control subjects.
For a detailed quantitative analysis, see Table 2. $*p < 0.001$, $**p < 0.05$

the ablation procedure and the variables of the filtered P waves were compared between those obtained before and after the catheter ablation.

### Statistical analysis

The variables were presented as the mean value $\pm$ the standard deviation. The statistical analyses were performed using the Mann-Whitney U test for comparisons of the total number of PACs, P on T type PACs, P on T type grouping PACs, and frequency of AF induced from P on T type PACs on the Holter monitoring. Student's $t$ test was used for statistical analyses of the structural variables, and for the FPD and RMS voltage of the SAECG variables. The level of statistical significance was determined as a p value of 0.05.

## Results

### Comparison of SAECG variables between the patients with and without AF

The clinical characteristics in the patients with and without AF (control) are comparatively shown in **Table 1**. Although the male gender is more predominant in the AF group, age and structural parameters of echocardiography did not differ between the two groups. In the micropotential variables of the SAECG (**Table 2**), the filtered P wave duration (FPD) was significantly longer in the patients with AF than in those in the control group ($133 \pm 12$ vs. $116 \pm 11$ msec, $p < 0.001$), and that is consistent with the previous reports.[1–3] The root-mean square voltage of the last 20 msec (RMS20) was significantly smaller in the patients with AF than in the control ($3.0 \pm 1.1$ vs. $5.1 \pm 1.9 \mu V$, $p < 0.001$) (**Table 2**, **Figure 2**), a finding consistent with a previous report.[1] However, neither the RMS30 nor RMS40 exhibited a significant difference between the two groups (**Figure 2**), although there have been no previous reports evaluating these variables. Representative SAECG records of patients with and without AF are demonstrated in **Figure 1**. The P waves in the control subjects (panel C) have an obviously shorter duration and greater amplitude of the last component of the P wave, as compared to that of the AF patients. One, as shown at panel A in **Figure 1**, exhibited amplitude of the last component of the P wave that was relatively high and almost comparable to that of the control group. Panel B (**Figure 1**) represents another characteristic the P wave, in which the amplitude of the last component of the P wave was relatively small.

### Comparison of the micropotential and clinical variables between the two subdivided groups in the patients with AF

Because the RMS30 was widely distributed
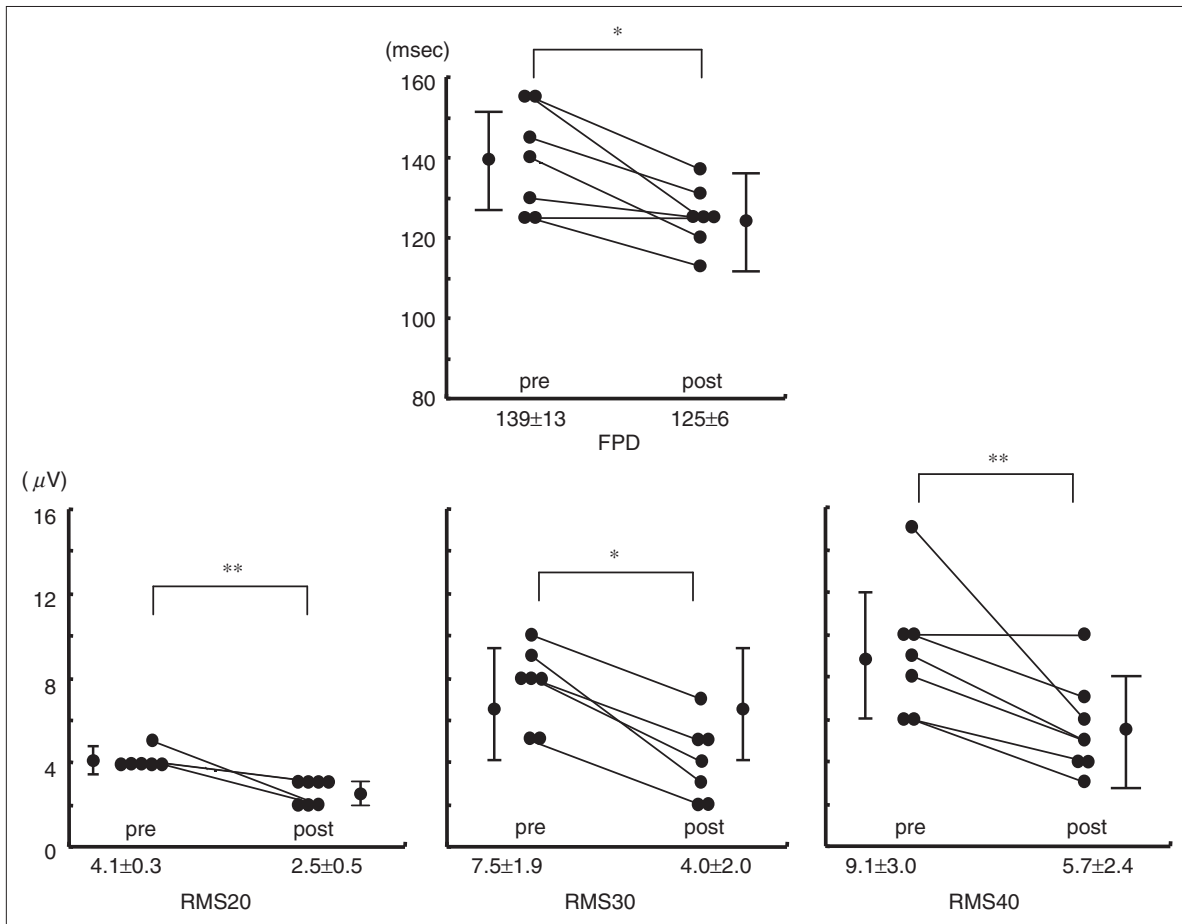


**Figure 3** Changes in the micropotential parameters before and after catheter ablation procedures.
Filtered P duration (FPD) was significantly shortened, and each of the RMS voltages exhibited a significant reduction after successful isolation of the PVs from the left atrial excitation. RMS20, 30, 40 = root-mean-square voltage of the last 20 msec, 30 msec, 40 msec of the signal-averaged filtered P-waves, respectively. *p < 0.001, **p < 0.05
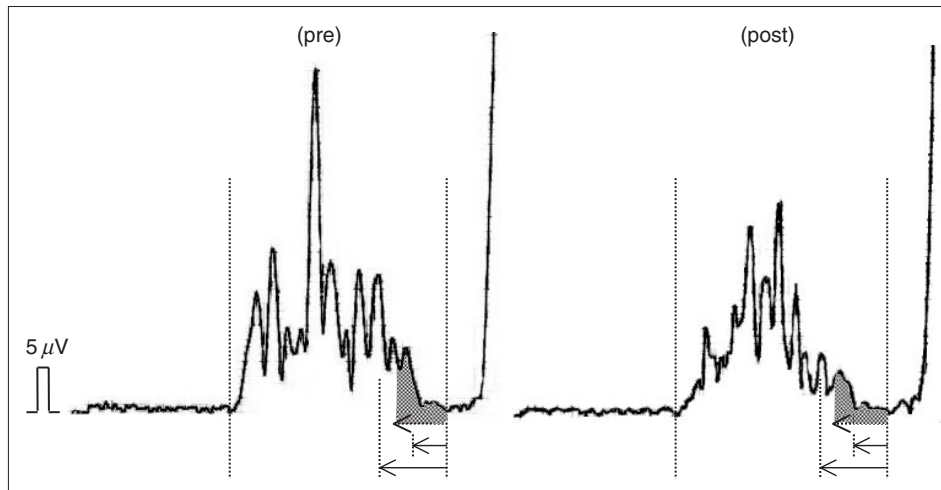
**Figure 4** A representative record of P-SAECG exhibiting significant changes in the micropotential parameters of the filtered P wave after the catheter ablation procedure of the pulmonary veins.
The left panel demonstrates the P waves recorded before the ablation. The right panel shows the recording after the procedure. The gray zone represents RMS30 which apparently decreased after the catheter ablation. The dotted lines indicate the beginning and terminal portion of the P wave and the point of the last 20, 30 and 40 ms respectively. The arrows show the timing of the 20, 30, and 40 ms from the terminal portion of signal-averaged P wave, respectively.

between 2 and 10 µV in the patients with AF, these patients were sub-divided into two groups according to the RMS30 data. Group 1 consisted of 30 patients (25 males and 5 females, mean age $59 \pm 11$ years) in whom the RMS30 was equal or more than $5.0\,\mu V$ (the mean value for the RMS30 of the AF patients) (representative record demonstrated in panel A, **Figure 1**). Group 2 was comprised of the remaining 21 patients (15 males and 6 females, mean age $62 \pm 7$ years) in whom the RMS30 was less than $5.0\,\mu V$ (representative record shown in panel B, **Figure 1**).

Each micropotential parameter was compared between group 1 and group 2 (**Table 2**). There were of course significant differences in the RMS30 and RMS40 between group 1 and group 2 (RMS30, $6.4 \pm 1.3$ vs. $3.1 \pm 0.7\,\mu V$, $p < 0.001$; RMS40, $8.2 \pm 2.2$ vs. $4.1 \pm 1.1\,\mu V$, $p < 0.001$, respectively) (**Figure 2**). The RMS20 did not show a significant difference between group 1 and group 2, and was less than $3.5\,\mu V$ ($3.2 \pm 1.4$ vs. $2.7 \pm 0.5\,\mu V$). The FPD also did not exhibit a statistically significant difference between the two groups.

The clinical characteristics were compared between the two groups (**Table 1**). Six patients in group 1 and 9 patients in group 2 could not undergo the exercise testing because of handicapped leg, history of cerebral vascular event and other causes.

There were no significant differences in the clinical variables including the age, gender, period of illness and structural parameters assessed by echocardiography (LVEF, LA area and RA area). The maximum duration of the documented AF was significantly shorter in group 1 than in group 2 ($0.8 \pm 0.2$ vs. $4.4 \pm 3.3$ hours, $p < 0.01$). The induction of the AF subsequent to the short-coupled (P on T type) PACs was more frequently documented in group 1 than in group 2. Accordingly, either AF or PACs were more frequently induced by exercise testing in group 1 than in group 2 (59% vs. 0%; $p < 0.01$, 83% vs. 0%; $p < 0.01$).

**The change in the signal averaged P wave after the successful electrical isolation of the LA-PV interface**

Seven patients of group 1 underwent catheter ablation procedures, and a total of 20 PVs (mean 2.9 PVs) were successfully disconnected from the left atrium. Clinical variables including age, gender, Holter's monitoring, Treadmill exercise test and echocardiography were similar to those of the remaining 23 patients of group 1. **Figure 3** shows the change in the micropotential variables before and after the catheter ablation procedure in 7 patients. Each RMS voltage for both the last 20, 30 and 40 msec of the signal-averaged P wave were significantly attenuated after the successful electrical isolation of the PVs (RMS20, $4.1 \pm 0.3 \rightarrow 2.5 \pm 0.5\,\mu V$, reduction rate $-39.0\%$, $p < 0.05$; RMS30, $7.5 \pm 1.9 \rightarrow 4.0 \pm 2.0\,\mu V$, reduction rate $-46.6\%$, $p < 0.001$; RMS40, $9.1 \pm 3.0 \rightarrow 5.7 \pm 2.4\,\mu V$, reduction rate $-37.3\%$, $p < 0.005$; respectively).

Specifically, the RMS30 demonstrated the most statistical significance. The FPD was also significantly shorter after the catheter ablation than that before ($139 \pm 13 \rightarrow 125 \pm 6$ msec, reduction rate $-9.8\%$, $p < 0.01$). The representative recordings of the signal-averaged P waves before and after the successful catheter ablation are shown in **Figure 4**. It is noted that the FPD became shorter and the amplitude of the last portion of P wave become smaller after successful electrical isolation of all 4 PVs in this case.

### Discussion

The major findings in the present study were as follows: (1) The filtered P wave duration (FPD) was significantly longer in the patients with paroxysmal AF than in the control subjects; (2) When the patients with AF were divided into two groups according to the value of the RMS30 (group 1: RMS30 $\geqq 5.0\,\mu$V, group 2: RMS30 $< 5.0\,\mu$V), the induction of the AF subsequent to the PACs was more frequently documented, and accordingly AF was more frequently induced by exercise in group 1 than in group 2; (3) After the culprit PVs were successfully isolated from the left atrium, the FPD significantly shortened, and each of the RMS variables significantly attenuated.

The P wave triggered signal-averaged electrocardiography has been investigated as a useful means for the detection of the risk of paroxysmal AF,[1,12–19] and the recurrence of AF after successful electrical restoration of sinus rhythm in patients with persistent AF.[2,3,20,21] The filtered P wave duration (FPD) has been shown to be longer in the patients with AF than in those without AF, and a value more than 120 msec[1] or 130 msec[3,20] has been an independent predictor for paroxysmal or recurrent AF. Similarly to those previous reports, in this study, the FPD was significantly longer in the patients with paroxysmal AF than in the control subjects. The root-mean-square (RMS) voltage of the terminal portion of the P wave has also been evaluated with respect to its usefulness as a predictor of AF emergence; however, there are few such reports. Fukunami et al.[1] found that an RMS voltage of the last 20 msec (RMS20) $< 3.5\,\mu$V might be a significant predictor for the occurrence of AF. Moreover, they showed that the combined use of both an FPD $> 130$ msec and RMS20 $< 3.5\,\mu$V is a more powerful predictor (positive predictive accuracy $= 83\%$). In our study, the RMS voltage of the last 20 msec (RMS20) was significantly less in the patients with AF (as a whole group including both group 1 and group 2) than in the control group, and this may correspond to

findings of the previous study. However, the RMS voltage of the last 30 and 40 msec was significantly greater in the patients with AF which was triggered by repetitive focal firing probably originating from the pulmonary veins (group 1), than in those patients without such a clinical feature (group 2). The mechanism underlying the substantial difference in the RMS voltage between two groups remains obscure.

Recently, AF mainly originating from PVs has gained clinical significance and has been shown to be curable by catheter ablation targeting the PV-LA connection.[22–24] Consequently, the histo-pathological evaluations of the PV sleeve musculature have gained the physician's interest. Out of a number of histo-pathological reports,[7–9] Kholová et al.[7] clearly demonstrated that the upper PVs have significantly longer and thicker extensions of the atrial myocardium in patients with AF as compared to those without AF. Tagawa et al.[8] also revealed important histological characteristics of the arrhythmogenic PVs. They showed that although the maximum distance of the myocardial sleeves in the upper PVs did not differ significantly between the patients with and without AF, the variability of the myocardial size and degree of interstitial fibrosis was significantly greater in patients with AF than in those without AF. In addition to the fibroid degeneration, the PV musculature has been shown to have an anisotropic fiber orientation,[4] which is a potent predisposing factor of a conduction disturbance.[25] In fact, Jäis et al.[25] clinically demonstrated the electrophysiological properties of PVs that PVs showed decremental conduction properties and significant shorter ERP and FRP in patients with AF than in those without AF.

Furthermore, it has been shown that an electrical connection of the PV musculature and left atrial muscle may be more fixed in patients with AF than in those without,[7–9] while there is sometimes no myocardial extension into PVs in the patients without a history of AF.[11] From these previous observations, the difference in the amplitude of the terminal portion of the filtered P wave, which was observed in the present study, might reflect structural differences such as the extent of the PV musculature, and conduction properties of both the LA-PV interface and PV musculature. The fact that the successful electrical disconnection of the PVs shortened the FPD and attenuated the RMS voltage of the terminal portion of the filtered P wave may support the mechanistic hypothesis that the excitation of the PV musculature itself contributes at least in a part to the formation of high-frequency signals, especially in

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the terminal portion of the P wave in the patients with AF.

### Study limitations

Our study had the following study limitations. First, we assessed the effect of catheter ablation on the micropotential variables of the SAECG in a small number of patients (n = 7) in whom PV-LA electrical disconnection was achieved for a mean of 2.9 out of 4 PVs at the end of the ablation session. However, the response of the FPD and RMS voltage was similar, and the left sided PV or PVs were successfully isolated where the excitation was supposed to be late during sinus rhythm, in all patients. Therefore, our findings are considered to be reliable and reproducible. Secondly, one might speculate that the last portion of the filtered P wave may also reflect the excitation of PVs in the normal subjects. However, we do not have any answer to this question, because we did not undertake PV isolation in any of the control subjects. Finally, any autonomic interference[26,27] (e.g. mental stress, such as that associated with intrinsic catecholamines) with the parameters during the SAECG recordings was not completely excluded.

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