Long-Term Follow-up of Changes in Fibrillation Waves in Patients With Persistent Atrial Fibrillation

— Spectral Analysis of Surface ECG —

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Background Little is known about the shortening of atrial refractoriness as a result of electrical remodeling in atrial fibrillation (AF) in clinical cases, especially in terms of long-term follow-up, because of a lack of noninvasive testing methods.

Methods and Results The present study population comprised 38 consecutive patients with persistent AF (PAF, >1 month). Before and after the follow-up period of 1–14 months, surface ECGs were recorded for analysis. In each case, the fibrillation wave was purified by subtracting the QRS-T complex template and then power spectral analysis was performed. The mean fibrillation cycle length (FCL) and FCL coefficient of variation (FCL-CV) were determined from peak power frequency in 20 epochs in each recording. The change in FCL (Δ FCL) was calculated by subtracting the baseline FCL from the FCL after the follow-up period. To correct for the difference in the follow-up period, Δ FCL was divided by the follow-up period in each case. In 38 cases, mean FCL decreased from 160 ± 20 ms to 151 ± 19 ms ($p < 0.05$), and the FCL-CV also decreased from $15 \pm 9\%$ to $12 \pm 5\%$ ($p < 0.05$). The corrected Δ FCL was -2.4 ± 7.6 (ms/month) and there was a significant negative correlation between corrected Δ FCL and baseline FCL ($p < 0.01$).

Conclusion Shortening of the FCL during a relatively long-term follow-up period was observed in patients with PAF. (Circ J 2006; 70: 169–173)

Key Words: Atrial fibrillation; Electrical remodeling; Fibrillation cycle length; Spectral analysis

Atrial fibrillation (AF) is one of the most common supra-ventricular tachyarrhythmias and its management is clinically important. Although the importance of triggering atrial arrhythmias, such as atrial premature contractions from pulmonary veins, has been emphasized in cases of AF,^{1,2} the mechanism of reentry is considered to be involved in its maintenance.^{3–6} The shorter the atrial wavelength, the more likely reentrant circuits for AF can exist; therefore, shortening atrial refractoriness might play a role in exaggerating AF.^{7–10} In accordance with experimental reports, it is expected that atrial refractoriness will be shortened as a result of atrial electrical remodeling, but little is known about this point in clinical cases, especially over long-term follow-up, mainly because of technical limitations; that is, there is not a practical method for the evaluation of atrial refractoriness, especially using a non-invasive technique.

As the fibrillation waves in the surface 12-lead ECG reflect atrial electrophysiological properties during AF,^{11–14} recent studies have reported the usefulness of analyzing

fibrillation waves by the f-f interval¹⁴ or spectral analysis of fibrillation waves^{15–19} for noninvasive evaluation of AF reentrant circuits. In the present study, we used spectral analysis to evaluate the atrial fibrillation waves in surface ECGs as a means of clarifying the changes in atrial electrophysiological properties in patients with persistent AF (PAF) over a relatively long-term period of observation.

Methods

Subjects and Basic Study Protocol

The study population was 38 patients with PAF who were treated in Kitasato University Hospital. PAF was defined as AF that could be terminated but was not self-terminating. The subjects had to satisfy the following criteria: (1) AF duration longer than 1 month, (2) clinical symptomatic level New York Heart Association class 1 or 2, (3) no myocardial infarction, revascularization or cardiac surgery in the previous year, and (4) no anti-arrhythmic therapy (ie, Vaughan Williams class I and III) for at least 5 drug half-lives. Concomitant control of the ventricular rate with a calcium-channel antagonist, β -adrenergic receptor antagonist and digitalis were permitted.

The patients were followed-up over 1 month and a digitized 12-lead ECG recording was performed before and after that period. The recording time in the day was fixed at 09.00–12.00 h to exclude the influence of autonomic nervous system activity. All patients underwent a physical examination and echocardiography (Hewlett-Packard, SONOS-5500, Tokyo, Japan) at baseline to exclude serious

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Fig 1. Spectral analysis of the fibrillation waves in the surface ECG of a 61-year-old man. (Left) Baseline data, (Right) data after the follow-up period was completed. The horizontal axis indicates the frequency and each trace indicates the power spectrum of fibrillation waves in each 4-s window. Time-series spectral analyses of the fibrillation waves are shown by 3-dimensional plot of the power spectra during a 41-s period. At baseline, the fibrillation cycle length (FCL) calculated from the peak frequency was 171 ms and the FCL coefficient of variation (FCL-CV) was 19%. After follow-up of 2 months, FCL and FCL-CV decreased to 148 ms and 8%, respectively.

Fig 2. Changes in fibrillation cycle length (FCL) (Left) and FCL coefficient of variation (FCL-CV) (Right) after the follow-up period. Each thin line indicates the change in the data in each case. (Closed circles) Mean data in each state with the SD bars. After the follow-up period, FCL and FCL-CV decreased significantly.

underlying disease. All study protocols were performed under the permission of the Ethics Committee of Kitasato University and written informed consent was obtained before study entry.

Analysis of Fibrillation Waves

Spectral analyses used data from the surface ECG lead V₁, which were digitally stored on-line on a microcomputer at sampling rate of 1 kHz, and the QRS-T complexes were subtracted using a template matching algorithm.¹⁵ Frequency analysis was performed off-line on a microcomputer (BIMUTUS II, Kissei Comtec Co Ltd, Matsumoto, Japan). Frequency analysis of the subtracted ECG involved 3 steps: (1) bandpass filtering, (2) application of a Hamming window and (3) 4096-point fast Fourier transformation. A 50% overlap of adjacent spectral analyses allowed the use of an average of 20 epochs of analyses within a single 44-s

data set.¹⁵ After spectral analysis, recordings were displayed as power spectra (Fig 1), which were quantified by measuring the peak frequency signal with the maximum magnitude derived from each epoch. The peak frequency of the spectrum in the 3–12 Hz range was converted to a cycle length (CL in ms = 1,000/frequency), defined as the fibrillation CL (FCL), averaged from 20 epochs. Temporal variability was expressed as the FCL coefficient of variation (FCL-CV) of 20 consecutive epochs. As the index for the change in FCL during the follow-up period, Δ FCL was calculated by subtracting the baseline FCL from the FCL after the follow-up period, and it was corrected by dividing by the follow-up period because each patient in the present study had a different follow-up period.

Statistical Analysis

All data are expressed as mean $\pm$ SD. A paired t-test was

Fig 3. Relationship between duration of atrial fibrillation (AF) and the fibrillation wave parameters: (A) baseline fibrillation cycle length (FCL), (B) baseline FCL coefficient of variation (FCL-CV) and (C) corrected Δ FCL. AF duration showed no significant correlation with any of the 3 parameters.

Fig 4. Relationship between corrected fibrillation cycle length (Δ FCL) and the other parameters. There was a significant negative correlation with baseline FCL ($p=0.003$), and a tendency towards a negative correlation with left atrial dimension (LAD), but it was not significant.

used for comparison between 2 groups and results were considered significant at $p < 0.05$.

Results

The mean age of the patients enrolled in this study was 67 ± 9 years old, and the female:male ratio was 11:27. Underlying heart diseases were ischemic heart disease (4),

cardiomyopathy (3), valvular heart disease (3), and other (1). None of the remaining 26 patients had structural heart disease. The duration of AF at the time of study entry was 73 ± 62 months (range 3–201, median 76 months). The mean left atrial dimension was 50 ± 9 mm (range 37–78) and the mean ejection fraction was $60 \pm 11\%$ (range 40–77). None of the patients suffered cardiac events during the mean follow-up period of 5 ± 3 (1–14) months.

Table 1 Comparison of Patients With Positive and Negative Δ FCL

	Negative Δ FCL (n=25)	Positive Δ FCL (n=13)	p-value
Baseline FCL	165 $\pm$ 21	152 $\pm$ 13	0.049
Baseline FCL-CV	18 $\pm$ 9	10 $\pm$ 5	0.003
Age (years)	69 $\pm$ 8	64 $\pm$ 8	NS
Gender (F/M)	9/16	2/11	NS
Existence of heart disease (no. (%))	7 (28)	5 (36)	NS
AF duration (months)	79 $\pm$ 61	61 $\pm$ 65	NS
Left ventricular ejection fraction (%)	60 $\pm$ 10	58 $\pm$ 12	NS
Left atrial dimension (mm)	52 $\pm$ 10	48 $\pm$ 7	NS

FCL, fibrillation cycle length; CV, coefficient of variation; AF, atrial fibrillation.

Fig 1 is a representative example of spectral analysis of the fibrillation waves and Fig 2 summarizes the data of the 38 cases. After follow-up, the FCL had significantly shortened from 160 $\pm$ 20 ms to 151 $\pm$ 19 ms ($p=0.01$) and the FCL-CV had also decreased from 15 $\pm$ 9% to 12 $\pm$ 5% ($p=0.03$).

Corrected Δ FCL was -2.4 ± 7.6 ms/month (range -25.8 to $+16.0$). As shown in Fig 3, there was no correlation between AF duration and the 3 fibrillation wave parameters (baseline FCL, baseline FCL-CV and corrected Δ FCL), although corrected Δ FCL showed a significant negative correlation with the baseline FCL (Fig 4A), but no correlation with left atrial dimension (Fig 4B).

Although the mean FCL was shortened overall in the present study, some cases showed prolongation during the follow-up period. Table 1 compares patients with negative Δ FCL ($n=25$) and positive Δ FCL ($n=13$). There was no significant difference between the 2 groups in sex, age, existence of heart disease, AF duration, left atrial dimension and LV ejection fraction. There were significant difference in baseline FCL (165 $\pm$ 21 ms vs 152 $\pm$ 13 ms, $p=0.049$) and baseline FCL-CV (18 $\pm$ 9% vs 10 $\pm$ 5%, $p=0.003$).

Discussion

The present evaluation of the FCL of relatively long-lasting PAF by frequency analysis revealed several interesting findings. First, mean FCL and FCL-CV decreased overall during a follow-up period of 1–14 months. Second, there was no correlation between AF duration and the baseline FCL, but the corrected Δ FCL, the index of change in FCL, showed a significant correlation with baseline FCL. Third, patients with negative Δ FCL showed longer FCL and larger FCL-CV at baseline than those with positive Δ FCL.

AF Duration and FCL Shortening

The results from experimental studies concerning electrical remodeling indicate that atrial refractoriness shortens over time in patients with AF, and clinical studies have documented that AF patients have shorter atrial refractoriness than controls.²⁰ However, because this shortening of atrial refractoriness appears to be time dependent, the longer the AF lasts, the shorter the atrial refractoriness should be and to clarify this assumption, atrial refractoriness has to be evaluated repeatedly, preferably non-invasively.

Clinically, it is considered that paroxysmal AF eventually develops into its chronic form.²¹ Bollman et al analyzed atrial fibrillation waves in the surface ECG in patients with paroxysmal (duration 1–665 min) and persistent (duration 3–24 months) AF and showed that the fibrillatory frequency of PAF was higher than that of paroxysmal AF (6.9 $\pm$ 0.5 Hz

vs 5.1 $\pm$ 0.7 Hz, $p<0.001$).¹⁷ Fujiki et al also used a similar system and reported that patients with PAF (>3 days) had a shorter FCL of 139 $\pm$ 16 ms than those with paroxysmal AF (178 $\pm$ 26 ms, $p<0.001$).¹⁸ In the present study, we found that FCL and FCL-CV still decreased in at least some patients with relatively long-lasting PAF, and this is the first report documenting long-term changes in fibrillation wave properties in the same patients over time.

Interestingly, AF duration did not correlate with baseline FCL at the time of study entry, although it showed significant shortening at the end of the follow-up period. There are 3 possible explanations. First, because the patients in the present study had relatively long-lasting AF, the shortening of the FCL might have been close to the nadir, so that the AF duration might not have had as strong an influence on FCL shortening as in patients with shorter duration AF. Second, because the measurement of FCL using surface ECG is strongly dependent on the recording of fibrillation waves, it could be influenced by other factors, such as body size, obesity, etc. However, because we compared data obtained from the same patients in the present study, these additional factors could be excluded and even small changes in FCL were documented in these patients. Third, cardio-active medications, such as digitalis or β -blockade, might affect the FCL, especially in the baseline evaluation. Although patients taking antiarrhythmic agents were excluded, the basic medications allowed in the present study might affect atrial refractoriness through their action on the autonomic nervous system.

Baseline FCL as a Predictor of FCL Shortening

We found a negative correlation between corrected Δ FCL and baseline FCL, which indicates that a larger decrease in FCL (larger negative Δ FCL) is expected in patients with longer baseline FCL and bigger temporal variation of FCL. Because shortening of FCL was not always observed, our study population may include some patients with heterogeneous electrophysiological properties. Additionally, because the baseline FCL and FCL-CV were the only factors that differed between the negative and positive Δ FCL patients, the change in FCL might be reflecting only a natural fluctuation in at least some cases. However, because the mean FCL was significantly shortened overall, it is possible to say that a population of patients with relatively long-lasting AF includes some who can show additional shortening of FCL (ie, progression of atrial electrical remodeling).

Our finding also seems to indicate the existence of a nadir of atrial refractoriness shortening as a result of atrial electrical remodeling. Although we observed that FCL still decreased in patients with relatively long-lasting PAF, the

FCL could not be shortened when it was very close to the nadir. The time to reach this point was unclear in the present study, but there seems to be individual variation because there was no significant relationship between corrected Δ FCL and AF duration.

Usefulness of Spectral Analysis of Fibrillation Waves in the Surface ECG

We used spectral analysis of fibrillation waves in the surface ECG, which has some benefits in comparison with the classical manual analysis of fibrillation waves, because the fibrillation waves in the surface ECG trace include very small deflections that manual or visual detection may include as human detection errors. In contrast, because spectral analysis of the digital ECG recording does not include human sampling error, it is a purely objective analysis of the fibrillation waves. Additionally, because the QRS-T waves are digitally subtracted from the original ECG traces, the result of the spectral analysis becomes more sensitive, especially for low-frequency data. However, to apply this intelligent method, the ECG traces must be recorded in a specific recorder, so ECG recordings made in other machines or previous print-based ECG traces cannot be used.

Study Limitations

First, although the study reached some conclusions, the results were from a relatively small number of patients. Second, subjects in this study included patients with organic heart disease and changes in their basic disease may have influenced the results. Third, the AF duration data were mainly obtained from the patient's history and ECG recording during a limited time, so asymptomatic AF or unknown conversion cannot be excluded. Fourth, temporal fluctuations of the FCL (eg, daily variation, influence of changes accompanying the underlying diseases and errors of measurement) can not be absolutely excluded.

Clinical Implications

This is the first report to document progressive shortening of the FCL in relatively long-lasting PAF, and the usefulness of spectral analysis for repeat evaluation of the fibrillation waves on ECG in the same patient. Our method can be used to monitor atrial refractoriness in patients with PAF, especially over the long term, and could assist in antiarrhythmic drug selection because of its focus on electrical remodeling.

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