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Original Article

Morphological Properties of Atrial Fibrillation Waves in Patients with Left Ventricular Dysfunction —Spectral Analysis of Atrial Fibrillation Waves in Dilated Cardiomyopathy—

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Introduction: Although the atrial fibrillation cycle length (FCL) is considered to shorten in persistent atrial fibrillation (AF) as a result of electrical remodeling, whether a long-term change remains in FCL in patients with left ventricular (LV) dysfunction is uncertain. Morphological properties of AF waves were analyzed in patients with dilated cardiomyopathy (DCM). Methods and Results: The study population consisted of 43 patients with persistent AF, and they were divided into a DCM group ($n = 14$) and a control group ($n = 29$). Fibrillation waves from surface ECG lead V1 were purified by subtracting the QRS-T complex template. Power spectral analysis was performed by Fast Fourier Transformation, and the mean FCL was determined by the peak power frequency in 20 epochs at each recording. The LV ejection fraction was lower in the DCM group ($50 \pm 18\%$) than the control ($63 \pm 8\%$, $p = 0.001$). The mean FCL was shorter in the DCM group (132 ± 14 ms) than the control (151 ± 23 ms, $p = 0.007$) and there was a significant correlation between the FCL and LV dimensions ($p = 0.03$). Conclusion: In patients with persistent AF and LV dysfunction, FCL was shorter in comparison with the control, and seemed to be influenced by LV dimensions.
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Key words: Atrial fibrillation, Electrical remodeling, Spectral analysis, Fibrillation cycle length, Dilated cardiomyopathy

Introduction

Atrial fibrillation (AF) is one of the most common forms of supra-ventricular tachyarrhythmia and is markedly more prevalent among heart failure (HF) patients than in the general population.[1)] Although the importance of triggering atrial arrhythmias, such as atrial premature contractions from pulmonary

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veins, has been emphasized in AF cases,[2,3] the mechanism of reentry is still important in its maintenance.[4–7]

As determinants for the reentry, the myocardial refractory period plays a key role, and electrical remodeling, i.e., the shortening of the atrial refractory period due to AF, is considered to exaggerate the AF itself.[8–11] In contrast, several investigators have reported a prolongation of, or no change in, the atrial electrophysiological properties (e.g., action potential duration) in heart failure cases,[12,13] probably due to the down-regulation of several potassium channels.[13] Therefore, it is unclear whether the atrial refractoriness would be prolonged or shortened in cases with AF and LV dysfunction because LV dysfunction and AF can exaggerate each other.

Intracardiac catheterization is the only direct measurement for evaluation of atrial refractoriness, but it is not appropriate for evaluating repeatedly or frequently in the clinical setting. Because the atrial fibrillation wave (f-wave) in a surface ECG reflects the complexity of activation wave fronts in the atria, analysis of the f-wave may give a useful parameter for the atrial electrophysiological properies.[14–20] In previous reports, fibrillation cycle length (FCL) calculated from spectral analysis of the f-waves in the surface ECG showed a significant correlation with atrial refractoriness.[19,20]

In the present study, we analyzed the f-waves in cases with persistent AF and LV dysfunction to clarify the influence of LV dysfunction on the atrial electrophysiological properties in AF cases.

Methods

Subjects

The study population consisted of 43 consecutive patients with persistent AF. Of the 43 patients, 14 had dilated cardiomyopathy (DCM group) as the basic heart disease and the remaining 29 patients did not have organic heart disease (control group). Persistent AF was defined as AF which can be terminated, but is not self-terminating. The continuation of the AF was confirmed by recording electrocardiograms three times during a 2–4 week period. For patient selection, the subjects had to satisfy the following criteria. (1) Clinical symptomatic level of New York Heart Association class 1–2. (2) No anti-arrhythmic administration (i.e., Vaughan Williams class I and III) for at least five drug half-lives. Concomitant control of the ventricular rate with a calcium channel antagonist, beta-blocker or digitalis was permitted. (3) Patients with renal dysfunction (serum creatinine levels >2.0 mg/dL) or severe liver dysfunction were excluded. Patients with DCM were diagnosed by cardiac catheterization including coronary angiography, left ventriculography and left ventricular biopsy. They were treated with medication in accordance with the guidelines for therapy of DCM, including angiotensin-converting enzyme inhibitors, beta-blockers or diuretics. The patients in the control group underwent physical examination and echo-cardiography to exclude any underlying structural disease.

Evaluation of the patients' basic status

Echocardiography was performed with SONOS 5500 (Hewlett-Packard, Tokyo, Japan) to evaluate the left atrial dimension, left ventricular (LV) ejection fraction, LV end-diastolic dimension and LV end-systolic dimension. Plasma B-type natriuretic peptide (BNP) concentration levels were measured in all patients except three in DCM and one patient in the control group. Blood samples for BNP were obtained at the time of ECG recording.

Recording of surface ECG and analysis of fibrillation waves

All patients underwent digitized 12-lead ECG recording at a steady state and all data were stored on-line on a microcomputer at a sampling rate of 1 kHz. The recording time of day was fixed between 9:00 and 12:00 am to exclude the influence of autonomic nervous system activation levels.

Out of the 12 lead ECG traces, the recording in V_1 lead was used in this study because the f-wave is usually most prominent in this lead. To obtain pure f-wave traces, a QRS-T wave template was made by a signal-averaged ECG, then the template was subtracted from the original ECG traces in the digital data.[18] Frequency analysis was performed off-line on a microcomputer (Bimutas II, KISSEI COMTEC Co. Ltd., Matsumoto, Japan). Frequency analysis of the subtracted ECG involved three steps including 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-sec data set.[18] After spectral analysis, recordings were displayed as power spectra. Power spectra 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) and defined the fibrillation cycle length (FCL) which was averaged from 20 epochs. Temporal variability was expressed as the FCL

coefficient of variation (FCL-CV) of 20 consecutive epochs.

All study protocols were performed with the permission of the ethics committee of Kitasato University and written informed consent was obtained before study entry.

Statistical analysis

All data are expressed as mean ± SD. An unpaired t-test was used to compare parametric parameters between the two groups and categorical parameters were compared using χ^2 analysis. The correlations between FCL and echocardiographic parameters were analyzed using all patient data and Pearson's simple correlation coefficient was used. Results were considered statistically significant at $p < 0.05$.

Table 1 Clinical characteristics of the patients.

	DCM (n = 14)	Control (n = 29)	
Age (years old)	58 ± 16	70 ± 8	p = 0.004
Gender (F/M)	2/12	8/21	NS
AF duration (months)	63 ± 52	61 ± 56	NS
LV ejection fraction (%)	50 ± 18	63 ± 8	p = 0.001
LV end-diastolic dimension (mm)	55 ± 8	51 ± 6	p = 0.04
LV end-systolic dimension (mm)	40 ± 9	33 ± 6	p = 0.002
Left atrial dimension (mm)	49 ± 7	49 ± 9	NS
BNP (pg/mL)	243 ± 363	150 ± 103	NS
Medications			
Digitalis	11 (79%)	21 (72%)	NS
Beta blocker	10 (71%)	8 (28%)	p = 0.02
ACE inhibitor	12 (86%)	6 (21%)	p = 0.0002

DCM = dilated cardiomyopathy; AF = atrial fibrillation; LV = left ventricular; BNP = B-type natriuretic peptide; ACE = angiotensin-coverting enzyme

Results

Table 1 summarizes the clinical characteristics of the patients in this study. There were significant differences between the two groups in echocardiographic data because differences in the basic heart disease. The number of beta-blocker or angiotensin-converting enzyme inhibitor prescriptions was higher in the DCM group than the control reflecting therapy for heart failure. There was no significant difference in other clinical background data except for patient age.

Figure 1 shows FCL and FCL-CV data in the two groups. The FCL was significantly shorter in the DCM group (132 ± 14 ms) than in the control group (151 ± 23 ms, p = 0.007), but there was no significant difference in the FCL-CV data between the two groups (DCM 12 ± 6% vs. control 13 ± 7%, NS).

Figure 2 shows the relationships between FCL data and the echocardiographic parameters. In each analysis, primary regression was calculated using all the data for the two groups. Although LAD did not show a significant correlation with FCL, left ventricular dimensions (LVDd and LVDs) showed a significant negative correlation with FCL. LVEF tended to show a very weak positive correlation with FCL, but it was not significant.

Because there were differences in age and med-

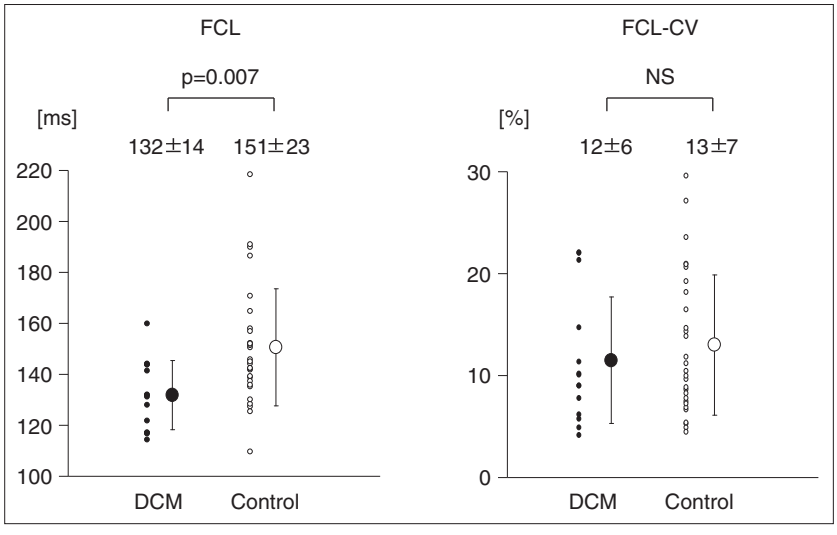

Figure 1 Comparison of FCL and FCL-CV data between the two groups.
This figure shows the FCL (left panel) and FCL-CV (right panel) data of the two groups. In each panel, small circles indicate the individual data and large circles with SD bars show mean data. FCL was significantly shorter in the DCM group (132 ± 14 ms) than in the control group (151 ± 23 ms, p = 0.007), but there was no significant difference in FCL-CV data between the two groups (DCM 12 ± 6% vs. control 13 ± 7%, NS). See text for discussion. FCL = fibrillation cycle length, FCL-CV = FCL coefficient of variation.

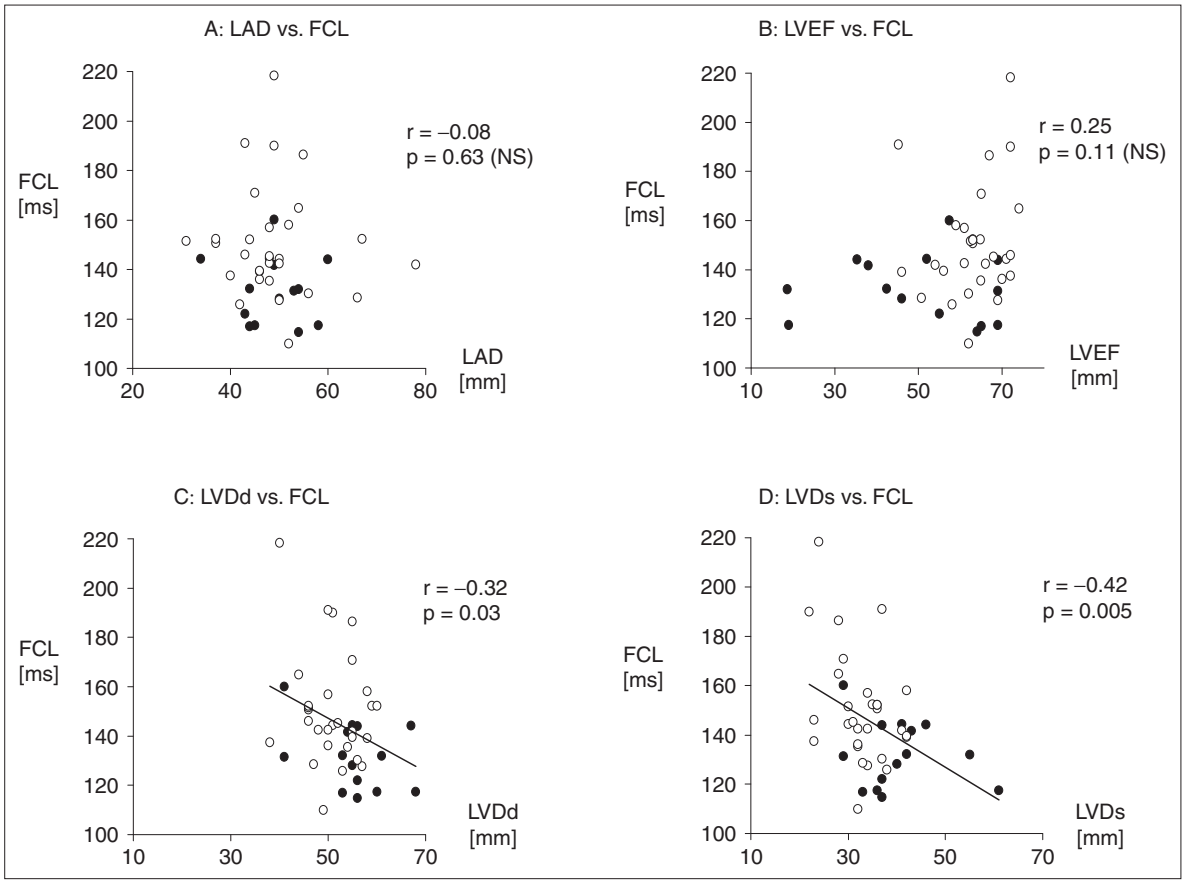

Figure 2 Relationships between FCL data and echocardiographic parameters.
This figure shows the relationships between FCL data and the echocardiographic parameters, i.e., left atrial dimension (LAD: panel A), left ventricular ejection fraction (LVEF: panel B), left ventricular end-diastolic dimension (LVDd: panel C) and left ventricular end-systolic dimension (LVDs: panel D). Closed circles indicate individual data of DCM patients and open circles show those of the control patients. In each analysis, primary regression was calculated among the whole data for the two groups and a regression line was drawn if it was significant. Although LAD did not show a significant correlation with FCL, LVDd and LVDs showed a significant negative correlation with FCL. LVEF tended to show a very weak positive correlation with FCL, but it was not significant. See text for discussion.
FCL = fibrillation cycle length.

ication between the two groups, the correlation between these parameters and FCL was also evaluated. In total, FCL and age tended to show a weak positive correlation ($r = 0.24$) but it was not significant ($p = 0.16$). There was no significant difference in the FCL between the two groups with and without medications of angiotensin-converting enzyme inhibitors and/or anigiotensin receptor blockers (138 ± 21 ms vs. 150 ± 22 ms, NS), beta-blockers (144 ± 27 ms vs. 145 ± 19 ms, NS), or calcium blockers (158 ± 21 ms vs. 141 ± 21 ms, NS).

Discussion

The present study evaluating the FCL in patients with persistent AF and LV dysfunction revealed some interesting findings. First, FCL was shorter in the DCM group than the control, although FCL-CV did not show a significant difference. Second, there were significant negative correlations between FCL and LV dimensions, although left atrial dimension or LV ejection fraction did not show significant correlations.

Spectral analysis of atrial fibrillation waves in surface ECG

Previous studies with experimental models reported that atrial refractoriness is shortened as a result of atrial electrical remodeling in an AF condition.[8–11] Although electrical remodeling is considered to occur even in clinical cases, little is known about this phenomenon, mainly because of the technical limitation in measuring the atrial effective refractory period (ERP). Measurement of

ERP using premature stimulus via a catheter is the standard method, but it is invasive and it is impossible to evaluate the ERP during AF.

Recent studies have reported a new method for noninvasive assessment of human AF cycle length using surface ECG with spectral analysis,[18–20] and a significant correlation between the frequency content of the surface ECG and the intracardiac electrograms. Therefore, spectral analysis of f-waves in surface ECG is a feasible method to evaluate the atrial refractoriness in humans, and it was used in this study to evaluate the electrical remodeling in patients with persistent AF. In the present study, we chose the V_1 lead recording for the analysis as did the previous studies, and as it was technically difficult to choose the lateral chest leads because of the low amplitude of the f-wave in these leads. Because of the distance from the cardiac surface, this recording seems to reflect the electrophysiologic properties of the right atrium and not the left atrium. Our results might be misleading if the right and left atrial conditions were different, but the patients in this study were considered to have similar conditions in the two atria upon diagnosis of DCM and long lasting AF.

LV dysfunction and atrial electrophysiological properties

Although several experimental reports documented the shortening of atrial ERP under continuous rapid atrial activation, i.e., AF,[8–11] other studies reported no change in ERP in heart failure. Li et al. studied the effect of rapid atrial pacing on atrial ERP in heart failure, and reported that the atrial ERP and wavelength were not affected by rapid pacing, whereas they were significantly shortened by rapid pacing in patients without heart failure.[12] The precise mechanism is unclear, but the down-regulation of the potassium channel, especially the transient outward current channel (Ito), which is triggered by an increased atrial wall stress, is considered to play an important role.[13]

Therefore, the result of the electrical remodeling trigged by AF and LV dysfunction is questionable, especially in clinical cases. Sanders et al. evaluated the atrial electrophysiological characteristics in patients with heart failure and reported that patients with heart failure demonstrated an increase in atrial ERP with no change in the heterogeneity of refractoriness.[21]

These results suggest that the LV dysfunction suppresses the shortening of atrial ERP in the process of atrial electrical remodeling in AF, and differ from the results of the present study. Our results indicate shortening of atrial ERP in patients with LV dysfunction, and that the shortening was even exaggerated by the presence of LV dysfunction. Because an increase in the LV dimension would lead to larger mitral regurgitation or higher end-diastolic pressure, it is reasonable to correlate it with more severe heart failure and a higher chance of AF in clinical cases. Therefore, if AF causes the shortening of atrial ERP, our result is quite reasonable.

The reason for the difference between the results of previous reports and the present study is unclear, but one possible explanation is the difference in the method for the ERP measurement. Because our study used the spectral analysis of the f-wave in the surface ECG, the recording might reflect plural simultaneous atrial activations; the shorter FCL in our study may reflect not only shorter ERP, but also more complicated atrial activations. It is also reasonable to assume a higher number of simultaneous wave fronts on the surface of an enlarged chamber. Because we studied DCM patients with LV dysfunction in this study, it is unclear whether this result was specific or nonspecific for patients with DCM. This point should be addressed by analyzing the data in patients with LV dysfunction due to causes other than cardiomyopathy.

Study limitations

There were a few limitations in this study. First, although the study reached a few conclusions, they were evaluated in a relatively small number of patients. Second, the AF duration data were mainly obtained from their history and ECG recordings over a limited time, so asymptomatic AF or unknown conversion cannot be excluded. Third, there were some differences in the clinical characteristics of the patients in the two groups (i.e., age or medications). Although there was no significant correlation between FCL and those parameters in total, it is unclear whether these factors could affect atrial electrical remodeling in clinical cases. Further studies are needed to answer to these questions.

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