Spectral Characteristics of Human Atrial Fibrillation Waves of the Right Atrial Free Wall With Respect to the Duration of Atrial Fibrillation and Effect of Class I Antiarrhythmic Drugs

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The aim of this study was to use fast Fourier transform analysis to clarify the characteristics of human atrial fibrillation (AF) waves with respect to the duration of AF and the effect of class I antiarrhythmic drugs. Twenty-two patients (10 paroxysmal AF, 12 persistent AF) without organic heart disease were studied by conventional electrophysiological methods. Electrograms were recorded from the right atrial free wall during AF and spectral analysis was performed for 35 s (16 consecutive 4096-ms epochs with 50% overlap) and the fibrillation cycle length (FCL) was calculated from the peak frequency. Mean FCL and SD were determined from 16-epoch data, and the temporal variability of FCL was defined as the SD of FCL. Paroxysmal AF had a longer mean FCL than persistent AF (178±26 ms vs 139±16 ms, p<0.001) and AF duration had a significant inverse correlation with mean FCL ($r=-0.79$, p<0.001). The temporal variability of FCL was significantly greater in paroxysmal AF than in persistent AF ($p<0.05$) and there was a significant positive correlation between the mean FCL and the temporal variability of FCL ($r=0.66$, p<0.001). In 8 of 18 patients given a class I antiarrhythmic drug (cibenzoline or procainamide), AF was terminated and in those patients the mean FCLs before administration of class I drugs were significantly greater than in patients without AF termination. With respect to mean FCL before drug administration, conversion occurred in 100% of patients with FCL $\geq$168 ms and in 17% of those with FCL <168 ms. A longer duration of AF shortens the mean FCL, which is consistent with atrial electrical remodeling. Class I drugs prolong the mean FCL above a critical level and will terminate AF, which can be estimated from the mean FCL before drug administration. (Jpn Circ J 2001; 65: 1047–1051)

Key Words: Antiarrhythmic drugs; Atrial fibrillation; Atrial remodeling; Spectral analysis

Several electrophysiological properties of the atria (ie, shortening of the action potential duration, decreased conduction velocity, enhanced anisotropic conduction, and increased spatial disparity of these parameters) promote the development of atrial fibrillation (AF) by enabling the atrium to accommodate the requisite number of propagating wavelets that ensure perpetuation of AF.1–3 Recently, both experimental and clinical studies have suggested that persistent rapid rates of AF produce a progressive shortening of the atrial refractory periods because of electrical remodeling4–6 and this atrial remodeling may play an important role in the self-perpetuation of AF. The persistence of AF and its response to antiarrhythmic drugs differ depending on the status of electrical remodeling.

AF is a complex arrhythmia that can be analyzed by different methodological approaches. Manual measurement of the fibrillation intervals can become difficult when the fibrillation waves are irregular and fragmented. The frequency content of a signal during AF has 2 components: the cycle length of the fibrillation and the intrinsic frequency characteristics of individual deflections of the atrial electrograms. Therefore, the power in a bandwidth from 4 to 12 Hz (83–250 ms) could correspond to the intrinsic frequency of successive atrial activity of human AF.7–10 The purpose of this study was to evaluate the spectral characteristics of AF with respect to duration and the effect of class I antiarrhythmic drugs by using fast Fourier transform analysis in patients without organic heart disease.

Methods

Subjects

The study group consisted of 22 patients (17 men, 5 women; average age, 60.1 years; range, 37–85 years) who had experienced sustained AF (lasting $\geq$30 min). In all patients AF was documented as the underlying arrhythmia at the time of palpitation and the duration of AF was quantified through symptoms and ECG recordings. Ten patients had paroxysmal AF defined as self-terminating AF $<3$ days and 12 patients had persistent AF defined as non-self-terminating AF lasting $\geq$3 days. In 3 patients whose attacks of AF were usually persistent, the duration of AF in the electrophysiological study was less than 3 days. All patients

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had a physical examination and underwent ECG, echocardiography, and biochemical and hematological testing (including thyroid hormone) and none had any organic heart disease.

**Electrophysiological Study**

All electrophysiological studies were performed by standard methods after informed consent was obtained. All antiarrhythmic agents were discontinued for at least 5 half-lives before the study. All antiarrhythmic agents were discontinued for at least 5 half-lives before the study. A standard 6Fr deflectable decapolar catheter with 2-mm interelectrode spacing and 10-mm inter-polar spacing was introduced via the femoral vein. Bipolar intracardiac electrograms filtered between 0.5 and 500 Hz were recorded and stored digitally on a Cardiolab system (Prucka Engineering, Inc, TX, USA) simultaneously with a 12-lead surface ECG. The distal bipolar electrogram positioned at the middle right atrial free wall was selected for frequency analysis because of stable catheter contact with the wall.

Stimulation was performed with a programmable stimulator (Nihon-Kohden SEC3102, Tokyo, Japan). Stimuli were delivered as rectangular pulses of 2 ms duration and twice the diastolic threshold. In 4 patients with paroxysmal AF, atrial extrastimulation or rapid atrial pacing induced AF. In the remaining 18 patients spontaneous episodes of AF were sustained at the time of the electrophysiological study. Class I antiarrhythmic agents were given intravenously to 18 patients: cibenzoline (1.7 mg/kg for 10 min) to 14 patients or procainamide (20 mg/kg for 10 min) to 4 patients. In one patient, infusion of procainamide had to be stopped at 10 mg/kg because of hypotension. Conversion to sinus rhythm was achieved in 8 patients with paroxysmal AF (6 patients given cibenzoline, 2 patients given procainamide). The average time of conversion to sinus rhythm was 12.4±5.5 min.

**Frequency Analysis**

Recordings of both the 12-lead ECG and the bipolar atrial electrograms at the right atrial free wall region were started 5 min before and finished 10 min after the end of injection of the class I drugs and were stored on optical disk in the Cardiolab system. In 4 patients with pacing-induced AF, recordings were started at least 30 min after the induction of AF. This system used a conventional digital sampling rate of 1024 Hz. The analyses of 35-s electrograms at 5 min before the start of drug infusion and 5 min after the end of drug administration were performed off-line on a microcomputer (ValueStar NX, NEC, Tokyo, Japan). In 4 patients whose AF terminated before the sampling point (5 min after the end of drug injection) sampling was started 45 s prior to AF termination.

Frequency analysis of the electrograms involved 3 steps: bandpass filtering, application of a Hamming window, and 4096-point fast Fourier transformation. A 50% overlap of adjacent spectral analysis allowed the use of averages of 16 epochs of spectral analysis within a single 35-s data set. After spectral analysis, recordings were displayed as power spectra (Figs 1, 2). These spectra were quantified by measuring the
peak frequency signal derived from each epoch. In cases of multi-modality, we compared the peak frequency with the maximum magnitude. The peak frequency of the spectrum in the 4–12 Hz range was converted to a cycle length (cycle length in ms = 1,000/frequency) and termed fibrillation cycle length (FCL). Mean FCL was calculated on the basis of 16 epochs of spectral analysis within a single 35-s data set. The temporal variability was expressed as the SD of FCL values on the 16 epochs within a single 35-s data set.

Statistical Analysis

All data, unless otherwise noted, are expressed as mean ± SD. The correlation between the duration of AF or the temporal variability of FCL and mean FCL was expressed by the linear regression lines (Log (days) or SD of FCL = A[mean FCL] + B; where A is slope and B is intercept). Paired and unpaired t tests were used for statistical analysis when 2 groups of results were compared. Results were considered to be statistically significant when p<0.05. All statistical analyses were performed with the Statview for Windows program (Abacus Concepts, Inc, CA, USA).

Results

AF Duration and Fibrillation Wave Characteristics

The mean duration of AF was 55.7±106 days (range, 30 min to 360 days). There was a significant inverse correlation between mean FCL and duration of AF (r=-0.79, p<0.001) (Fig 3). Because the data were skewed, log-transformation of components of duration of AF (days) was performed. Patients with paroxysmal AF had a mean FCL of 178±26 ms (range, 135–215 ms), which was significantly longer than that of patients with persistent AF (mean, 139±16 ms; range, 116–162 ms; p<0.001). There was a significant positive correlation between the mean FCL and the temporal variability defined as SD of FCL (r=0.66, p<0.001) (Fig 4). The temporal variability of FCL was significantly greater in paroxysmal AF than in persistent AF (15.2±6.3 ms vs 10.3±3.0 ms, p<0.05).

Effects of Class I Antiarrhythmic Drugs on AF

In 8 of 18 patients given class I drugs, AF terminated within 10 min of the end of drug administration. The mean FCL increased significantly from 161±29 to 207±34 ms (p<0.001), but the temporal variability of FCL decreased significantly from 15.1±5.7 to 11.1±5.6 ms (p<0.05) (Fig 2). In patients in whom AF was terminated, mean FCLs before drug administration were significantly greater than in patients whose AF was not terminated (Table 1). When the baseline mean FCL was 168 ms or more, class I drugs converted AF to sinus rhythm in 100% of patients and when FCL was less than 168 ms, termination of AF occurred in 17% (Fig 5). With respect to the mean FCL after drug administration, conversion occurred in 88% of patients with a FCL ≥210 ms and in 10% of those with FCL <210 ms. In patients whose AF was not terminated, the temporal variability of FCL decreased significantly after the administration of class I drugs (Table 1).

Discussion

In the present study, there was a significant inverse correlation between the duration of AF and the mean FCL. Paroxysmal AF had a longer mean FCL and greater temporal variability than persistent AF. Termination of AF with class I drugs correlated with prolonged mean FCL before drug administration. After drug administration, the temporal variability of FCL decreased significantly only in those patients whose AF had not been terminated. These results suggest that (1) a longer duration of AF shortens the mean FCL, probably because of atrial remodeling; (2) class I antiarrhythmic drugs will terminate AF if the mean FCL is prolonged over critical level; and (3) changes in the temporal variability of FCL may also play a role in termination of AF.

Spectral Analysis of AF

Precise manual measurement of the fibrillation intervals during AF become difficult when the atrial activation is very irregular and the electrograms are fragmented. Slocum et al reported that the power spectrum of human AF has a discrete peak in the 4–9 Hz band, and Karagueuzian et al analyzed the frequency characteristics of canine AF and revealed both a discrete narrow band peak and a continuous broadband of the power spectrum. These studies suggested that quantitative evaluation of irregular fibrillation intervals could be possible with frequency analysis of fibrillation electrograms. Recently, Skanes et al suggested that during AF induced in an isolated sheep heart with acetylcholine...
perfusion, the multiple narrow-band peaks of power spectrum in the right atrium resulted from the ratio of the frequency activation from the source of periodic activity in the left atrium.\(^1\)

Holm et al developed a new method for noninvasive assessment of humane AF cycle length using a surface ECG with spectrum analysis.\(^2\) They analyzed the frequency characteristics of AF using QRST subtraction methods, but they did not find any differences in the AF cycles lengths with respect to the type or duration of AF. Bollmann et al also studied a technique for quantifying the frequency spectrum by surface ECG during AF and demonstrated that the episodes of AF that terminated in less than 5 min had a longer FCL than those that persisted for more than 5 min (183 ms vs 149 ms).\(^3\) In the present study, we found that paroxysmal AF had a longer mean FLC with a greater temporal variability than persistent AF, and we also found an inverse correlation between the duration of AF and mean FCL in patients who did not have organic heart disease (Fig. 3). This correlation presents two possibilities: one is atrial remodeling because of AF persistence and the other is longer duration of AF because of shorter mean FCL. Several studies have shown that during AF the atria undergo electrical and structural remodeling, including shortening of the FCL, interstitial fibrosis and enlarge-\(^ment\(^6\) which promote the continuation of AF, although the cause-and-effect relationship is still unclear.

We used semi-automatic measurements that allowed the analysis of AF in periods of longer duration (35 s equivalent to 220 consecutive atrial beats). Capucci et al reported that the mean of 100 consecutive FF intervals during AF showed a good correlation with atrial refractoriness, and they suggested that a certain number of FF intervals is required to obtain the representative character of the atrial activation during AF.\(^1\) In the present study, spectrum analysis of a longer period of AF enabled us to have a reliable measurement of FCL and the temporal variability of FCL, which showed a positive correlation (Fig. 4).

Wells et al reported that the configuration of AF electro-\(^grams\(^ changed from moment to moment, appearing more or less organized at different times.\(^1\)\(^4\) Previous mapping studies have revealed that the temporal and spatial vari-\(^ations\(^ in AF electrograms reflect the specific patterns of conduction, such as slow conduction, functional conduc-\(^tion\(^ block and pivot points.\(^1\)\(^5\)\(^6\) During AF the wavelet circulates around a line of functional conduction block and makes a sharp U-turn at the pivot points. The size of the functional circuits may change from time to time. The source of the activation wavefronts may be transient in themselves and the route of propagation from a source may change because of interactions with other wavefronts. Although we could not estimate the conduction pattern of the fibrillation waves from the peak frequency, the increase in the temporal variability of FCL may represent the insta-\(^bility\(^ of AF perpetuation because paroxysmal AF had a greater temporal variability of FCL than did persistent AF.

Mechanism of Termination of AF With Class I Drugs

Observations from mapping data of antiarrhythmic drugs used to terminate AF in dogs suggest that the increase in FCL by antiarrhythmic drugs may relate to fusion of wavelets, increase in the size of reentry circuits, decrease in circuit number, and thus termination of AF.\(^1\)\(^7\) Shimizu et al observed a discrete peak of the power spectrum of vagally induced canine AF at 17 Hz, which shifted to 7 Hz prior to the end of AF after the termination of vagal stimulation.\(^8\) Bollman et al reported that FCL was an accurate predictor of conversion of AF with ibutilide, and the success rate was 100% in patients with FCL >166 ms vs 29% in patients with FCL <166 ms.\(^1\)\(^0\) In the present study we found that FCL ≥168 ms before drug administration and FCL ≥210 ms after drug administration were accurate predictors of termina-\(^tion\(^ of AF with class I drugs. However, Sih et al observed that in 3 of 15 episodes, the AF cycle length decreased just prior to termination and they suggested that an increase in AF cycle length is not a universal precursor to termination.\(^1\)\(^9\)

Shima et al reported that prolongation of post-repolariza-\(^tion\(^ refractoriness by procainamide infusion is an impor-\(^tant\(^ factor in the termination of AF.\(^2\)\(^0\) Wijffels et al studied the antifibrillatory action of class I and III drugs in a goat model of chronic AF and found that cibenzoline increased the refractory period, decreased conduction velocity and did not change wavelength. However, it prolonged the FCL, widened the excitable gap and terminated AF. According to the multiple wavelets hypothesis, the number of wavelets varies as a result of variation in the rate of wave formation and extinction. Drugs that decrease the number of wavelets widen the excitable gap and may increase the temporal variability because the waiting time for reexcitation by another wavelet becomes longer and irregular. In the present study, termination of AF with class I drugs correlated with the prolongation of FCL. Interestingly, in patients who did not experience AF termina-\(^tion\(^, the temporal variability of FCL decreased signifi-\(^cantly\(^. We are unsure about the electrophysiological meaning of the temporal variability of FCL. Each dominant FCL may represent the presence of a relatively stable func-\(^tional\(^ reentry and so we believe that the destabilization of functional reentry, which may be related to the termination of AF, may increase the temporal variability. These observ-\(^ations\(^ suggest that not only FCL, but also the temporal variability of FCL, may play a role in AF termination.

Study Limitations

First, the correlation between FCL and termination of AF with class I drugs was evaluated in a relatively small number of patients. A larger sample with different antiar-\(^rhythmic drugs may be needed to confirm the present find-\(^ings\(^. Second, we did not evaluate atrial electrograms from different atrial sites. Third, we selected patients without organic heart disease and it is possible that patients with different underlying heart disease may have different spectral characteristics of AF. Fourth, the duration of the AF episodes was quantified mainly through each patient’s symptoms and asymptomatic episodes could not be entirely excluded.

Clinical Implications

In Japan, AF is a common arrhythmia requiring treat-\(^ment\(^ and, as is the case in other countries, it increases the risk of thromboembolism.\(^2\)\(^2\) AF may have different responses to antiarrhythmic drugs depending on the electrophysiological factors predisposing to it.\(^2\)\(^3\) In the present study of AF in patients without organic heart disease, we found specific spectral characteristics of AF depending on its duration. From the mean FCL and its temporal variability before and after drug administration we could estimate the possibility of termination of AF with antiarrhythmic drugs. The findings from spectral analysis of intracardiac
Spectral Analysis of AF Waves

References