Role of Fibrillation Cycle Length in Spontaneous and Drug-Induced Termination of Human Atrial Fibrillation

—— Spectral Analysis of Fibrillation Waves From Surface Electrocardiogram ——

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The aim of this study was to investigate the mechanism of spontaneous termination of atrial fibrillation (AF) by comparing it with drug-induced termination on the basis of changes in fibrillation cycle length (FCL). Fast Fourier transform analysis was carried out on the electrocardiogram (ECG) records of 27 patients with paroxysmal AF without organic heart disease. In 8 patients with drug-induced termination of AF, spectral analysis of the data from surface ECG lead V1 was performed before and after class I antiarrhythmic drug infusion for 10 min. In 19 patients with spontaneous termination of AF, the analysis used the Holter ECG recordings at 10 min before the spontaneous termination and at the termination. FCL was calculated from the peak frequency of each epoch and the mean FCL and the coefficient of variation (CV) of FCL were determined from the data of 20 epochs. In the 8 episodes of drug-induced AF termination, the mean FCL increased significantly with class I drugs (from 151±17 to 203±21 ms, p<0.001), whereas in the 19 episodes of spontaneous termination, the mean FCL and CV of FCL at termination did not differ from those at 10 min before the termination. Of the 19 episodes, 10 episodes terminating in the morning showed a significant increase in the FCL of the last epoch of the termination period (from 158±22 to 172±17 ms, p<0.05). In the 9 episodes terminating in either the afternoon or the evening, the FCL of the last epoch did not change significantly. Although drug-induced termination of paroxysmal AF may depend on a gradual increase in FCL, the pattern of spontaneous termination may depend on the time of day. Spontaneous termination in the morning may be caused by an abrupt increase in FCL related to vagolytic autonomic balance. (Circ J 2003; 67: 391–395)

Key Words: Antiarrhythmic agents; Atrial fibrillation; Fibrillation cycle length; Spectral analysis

A persistently rapid rate of atrial excitation produces a progressive shortening of the atrial effective refractory period and promotes the perpetuation of atrial fibrillation (AF);1,2 however, most paroxysmal AF terminates spontaneously within a few days despite the presence of atrial remodeling. Termination of human AF with class I antiarrhythmic drugs is preceded by an increase in fibrillation cycle length (FCL), and a failure to increase the FCL correlates with a failure to terminate the AF with medication.3 In canine models of AF, the mapping data suggest that the increase in FCL induced by antiarrhythmic drugs may relate to fusion of wavelets, an increase in the size of reentry circuits, a decrease in circuit number and finally, termination of AF.3

Located with drug-induced termination, the mechanism of spontaneous termination of human AF is still unclear. It is difficult to obtain intracardiac recordings just prior to spontaneous termination of paroxysmal AF for analysis of the fibrillation waves because spontaneous termination of AF can not be predicted accurately. To clarify the mechanism of termination of paroxysmal AF, we analyzed the fibrillation waves from the surface electrocardiogram (ECG) (Holter ECG and 12-lead ECG) during either spontaneous or drug-induced termination of AF in patients without organic heart disease and compared the spectral characteristics.

Methods

Subjects
The 27 patients with paroxysmal AF without organic heart disease were divided into 2 groups: (1) a drug-induced termination group comprising 8 consecutive patients (8 men; average age, 60.3±6.7 years) who underwent 12-lead ECG recordings before and after drug administration during medical termination of AF; and (2) a spontaneous termination group comprising 19 consecutive patients (15 men, 4 women; average age, 63.6±9.5 years) who were undergoing Holter ECG recordings at the time of spontaneous termination of the AF. All patients had had paroxysmal AF defined as self-terminating AF within 3 days, and the duration of AF had been quantified through ECG recordings (mean duration, 293±281 min; range, 31–1,220 min). All 27 patients had a physical examination and underwent 12-lead ECG, echocardiography, and biochemical and hematological testing. None had any underlying heart
disease except for 1 patient with vasovagal syncope, 2 patients with sick sinus syndrome and 2 patients with hypertension.

**Frequency Analysis**

**Drug-Induced Termination of AF** Spectral analysis used data from the surface ECG lead V1 that were digitally stored on a Cardiolab system (Prucka Engineering, Inc TX, USA). The analyses were performed for 10 min just before the start of class I antiarrhythmic drug administration (1.4 mg/kg cibenzoline in 5 patients, 10 mg/kg procainamide in 3 patients) and just after the end of the infusion. In each patient the AF terminated within 10 min of the end of drug administration.

**Spontaneous Termination of AF** Episodes of AF lasting longer than 30 min were selected if they spontaneously terminated during 24-h Holter ECG monitoring. The recordings from standard lead CM1 were displayed using a Holter ECG analyzer (SCM6000, Fukuda-denshi, Tokyo, Japan). In order to assess the temporal pattern of the fibrillation waves, the analyses of 41 s electrograms at 10 min before the termination and at the termination were performed offline on a microcomputer (Value Star NX, NEC, Tokyo, Japan). The ECG segments selected for analysis from the ECG lead V1 and the Holter ECG lead CM1 were digitized at a sampling rate of 1 kHz. The QRST complexes were subtracted using a template-matching algorithm. In each patient only 1 spontaneous episode of AF was analyzed.

Frequency analysis of the subtracted electrograms involved 3 steps: bandpass filtering, application of a Ham-
Drug-Induced and Spontaneous Termination of AF

Representative Cases of Drug-Induced and Spontaneous Termination of AF

Representative subtracted ECG recordings with corresponding spectral analyses from a patient with drug-induced termination are shown in Fig. 2. The peak frequency of each epoch shifted leftward after intravenous administration of cibenzoline. Representative ECG recordings with spectral analyses from a patient with spontaneous termination of AF in the morning are shown in Fig. 3. The peak frequency of each epoch did not show any significant shift between 10 min before and at termination. Only the peak frequency of the last epoch of the termination period shifted leftward.

Differences in Fibrillation Wave Characteristics Between Drug-Induced and Spontaneous Termination of AF

In the 8 patients with drug-induced termination, the mean FCL increased significantly from 151±17 to 203±21 ms with the class I drugs (p<0.001) (Fig. 4, left panel), but the CV of the FCL did not change significantly (9.6±21 ms with the class I drugs (p<0.001) (Fig. 4, left panel), but the CV of the FCL did not change significantly (9.6±21 ms vs 10.0±4.1%) (Fig. 4, right panel). In the 19 patients with spontaneous termination, the mean FCL and the CV of the FCL at the termination period did not differ significantly from those at 10 min before the termination (FCL: 165±20 vs 166±21 ms, CV: 11.5±4.0 vs 11.6±4.3%) (Fig. 4, left and right panels).

Results

Statistical Analysis

All data are expressed as mean±SD. Paired and unpaired t tests were used for comparison of the 2 groups of results. 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, Calabasas, CA, USA).

3.3 vs 10.0±4.1%) (Fig. 4, right panel). In the 9 episodes terminating in either the afternoon or the evening, the FCL of the last epoch of the termination period did not change significantly (Fig. 5, right panel).

Discussion

The present study demonstrated that spontaneous termination of paroxysmal AF occurs without a significant increase in the mean FCL at termination, whereas drug-induced termination of AF is preceded by a gradual increase in the mean FCL. In addition, spontaneous AF termination in the morning showed an abrupt increase in the FCL of the last epoch of the termination period. These results suggest that the role of FCL in spontaneous termination may be different depending on the time of day.

Spectral Analysis of AF

During AF, precise manual measurements of the fibrillation intervals would be difficult when the atrial activation becomes very irregular and electrogams are fragmented5 Slocum et al reported that the power spectrum of human intracardiac fibrillation waves has a discrete peak in the 4–9 Hz band6 and in our previous study, we found that the specific spectral characteristics of intracardiac fibrillation waves depended on the duration of AF in patients without organic heart disease7.

A new method for noninvasive assessment of the human AF cycle length using surface ECG with spectral analysis has been reported8,9 The frequency characteristics of fibrillation waves from the surface ECG are analyzed using QRST subtraction methods and a significant correlation between the frequency content of the surface ECG and the intracardiac electrograms has been observed during AF.
Therefore, spectral analysis of the surface ECG in AF could become a useful method for quantification of the fibrillation wave characteristics.

Mechanism of Termination of AF

Bollman et al reported that the FCL was an accurate predictor of the conversion of AF with the class III antiarrhythmic drug ibutilide? and in our previous study, we found that the mean FCL of more than 168 ms at the right atrial free wall before drug administration was a good predictor of AF termination with class I antiarrhythmic drugs. In the present study, drug-induced termination of AF was preceded by a remarkable increase in the mean FCL derived from the surface ECG, which was the same as the mean FCL derived from intracardiac electrograms.

Wijffels et al studied the antifibrillatory action of class I and class III drugs in a goat model of chronic AF. Cibenzoline increased the refractory period, decreased the conduction velocity and did not change the wavelength, but it prolonged the FCL, widened both the temporal and spatial excitable gaps and terminated AF. According to the multiple wavelets hypothesis, the number of wavelets varies with the variation in the rate of wave formation and extinction. A decrease in the number of wavelets induced by antiarrhythmic drugs may increase the FCL and thus increase the possibility of termination of AF. We considered that the increase in the temporal excitatory gap by antiarrhythmic drugs might accentuate the temporal variability of FCL before AF termination. We therefore measured the temporal variability using the CV of the FCL, but we did not find that it significantly increased before AF termination.

Several studies have shown that during AF the atria undergo electrical and structural remodeling, which includes FCL shortening, interstitial fibrosis and enlargement of the atria, that promotes the continuation of AF.12–14 However, the mechanism of spontaneous termination of AF is still unclear. A change in vagal activity is one possible mechanism because decreased vagal tone promotes a shortened atrial refractory period and terminates AF.15,16 In the present study, half of the spontaneous terminations occurred in the morning and were associated with an abrupt increase in the FCL of the last epoch of the termination period. In the morning, the autonomic balance usually shifts to the combination of decreasing vagal tone and increasing sympathetic tone, so it is possible that the abrupt increase in the FCL just before AF termination is caused by the vagolytic autonomic balance.

On the other hand, spontaneous termination in the afternoon or the evening did not show any significant changes in the FCL of the last epoch of the termination period. Sih et al observed that the AF cycle length decreased just prior to spontaneous termination in 3 of 15 episodes of AF and they suggested that an increase in AF cycle length is not a universal precursor to AF termination. Spontaneous termination of AF occurring without any appreciable increase in the mean FCL indicates that maintenance of this type of AF is not dependent on multiple wavelets and may instead depend on focal mechanisms related to automatic activities from the pulmonary veins.

Study Limitations

Spontaneous and drug-induced termination of AF were both evaluated in a relatively small number of patients without apparent organic heart disease. Spontaneous termination of AF in patients with congestive heart failure may have different fibrillation wave characteristics and so a larger sample of episodes of AF termination, including those with different underlying atrial electrophysiological backgrounds, is needed. Second, we did not evaluate the relationship between the surface ECG and the intra-atrial electrograms, but previous studies have indicated clearly that the frequency content of surface ECG correlates with that of intracardiac electrograms during AF.

Conclusions

The mechanisms of spontaneous and drug-induced termination of AF may differ. The pattern of spontaneous termination is not uniform, and AF termination in the morning may be caused by a vagolytic autonomic balance.

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References


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