Drug-Induced Changes in Fibrillation Cycle Length and Organization Index Can Predict Chemical Cardioversion of Long-Lasting Atrial Fibrillation With Bepridil Alone or in Combination With Aprindine

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Background The aim of this study was to investigate whether drug-induced changes in fibrillation wave characteristics can predict pharmacological conversion of long lasting persistent atrial fibrillation (AF).

Methods and Results The study group comprised 23 consecutive patients with AF lasting ≥1 month. Patients first received bepridil (200 mg/day) for 2–4 weeks. When sinus rhythm was not restored with bepridil, oral aprindine (40 or 60 mg/day) was added to bepridil. Fast Fourier transform analysis of fibrillation waves using lead V1 was performed to calculate the fibrillation cycle length (FCL). The spectral areas were measured and the maximum area divided by the total area was termed the fibrillation organization index (FOI). Sinus rhythm was restored in 16 of 23 patients (70%); 8 of these 16 patients received only bepridil (Group I) and the other 8 responders received bepridil and aprindine (Group II). In Group I bepridil increased both FCL (p<0.001) and FOI (p<0.001) and terminated AF after 20±12 days. In Group II bepridil increased FCL (p<0.005) and FOI (p<0.005) within 19±8 days. In the remaining 7 patients who did not have restoration of sinus rhythm, bepridil increased both FCL and FOI significantly, but less than in Group I, and the addition of aprindine did not further increase either of them. Chemical cardioversion of AF occurred in all patients with FCL ≥190 ms and FOI ≥45% after drug administration.

Conclusion Bepridil alone or in combination with aprindine converted long lasting persistent AF in association with an increase in both FCL and FOI. The combination of FCL and FOI after drug administration is helpful in predicting chemical cardioversion of persistent AF. (Circ J 2004; 68: 1139–1145)

Key Words: Antiarrhythmic drugs; Atrial fibrillation; Bepridil; Defibrillation; Spectral analysis

Most patients with long-lasting persistent atrial fibrillation (AF) have preceding paroxysmal AF1 and the usual treatment strategy is heart rate control, although restoration of sinus rhythm (SR) can be more desirable.2 Chemical cardioversion is effective for terminating AF that has lasted only a few days, and is of little help for the termination of long-lasting AF because of the remodeling that has occurred in the AF substrate. However, we have demonstrated that oral administration of bepridil alone or in combination with aprindine restored and maintained SR in 30% and 60%, respectively, of patients with long-lasting persistent AF (>3 months).3,4

Bepridil hydrochloride, a diarylaminopropylamine derivative, was introduced as a Ca antagonist affecting both L and T type Ca channels5,6 with a lidocaine-like fast kinetic block of the Na current.7 Recent reports have demonstrated that bepridil has unique electrophysiological properties that inhibit several types of K current, including the rapid, slow and ultra-rapid components of delayed rectifier K currents, at therapeutic concentrations (0.5–4 μmol/L).8,9 and it is expected to be effective for the termination of AF. As a class I antiarrhythmic drug, aprindine blocks the Na channel mainly in the inactivated state with intermediate onset and offset kinetics of use-dependency, but it is also effective for atrial arrhythmias10. Although a combination of bepridil and aprindine can terminate persistent AF, it takes approximately 1 month to convert to SR. Hence, this study was designed to investigate whether drug-induced changes in the spectral characteristics of the fibrillation waves can predict cardioversion of long-lasting persistent AF.

Methods

Subjects
This study included 23 consecutive patients (17 men, average age 59±10 years) with persistent AF who had symptoms and desired restoration of SR. All patients had had persistent AF lasting at least 1e month. The duration of AF had been quantified by ECG recordings, and was 46±64 months on average (range: 1–240 months). All 23 patients had a physical examination and underwent 12-lead ECG, echocardiography, and biochemical and hematological
testing. Exclusion criteria included age >80 years, women of childbearing age, myocardial infarction, or revascularization within 3 months, left ventricular ejection fraction (LVEF) <0.35, QTc of >0.46 s, serum K <3.8 mmol/L, or a history of sick sinus syndrome. All patients underwent anticoagulation therapy with warfarin (international normalized ratio 2.0) for at least 4 weeks before chemical cardioversion. Concomitant control of the ventricular rate with Ca antagonists, β-blocking drugs or digitalis was permitted.

**Study Protocol**
After informed consent was obtained, a low dose of oral bepridil (100 mg/day) was administered for 1–2 weeks. If there was no abnormal prolongation of QTc to ≥0.50 s or by ≥25% of the baseline value, then oral bepridil (200 mg/day) was started and patients were followed for 2 or 4 weeks. If bepridil failed to restore SR and the QTc interval was not abnormally prolonged, oral aprindine (60 mg/day if body weight ≥70 kg or 40 mg/day if body weight <70 kg) was added to the bepridil (200 mg/day) and patients were followed for another 4 weeks.

**ECG Measurements**
Twelve-lead ECGs were recorded at a paper speed of 25 mm/s. QT intervals that spanned the onset of the QRS complex to the end of the T wave were determined from the lead with the longest QT interval, and the same lead was used for serial measurements in each patient. The point at which the tangent drawn to the steepest portion of the down-sloping T wave intersected the isoelectric line was used as the end of the T wave. During SR and AF, the QT interval was corrected (QTc) by dividing by the square root of the preceding RR interval that showed the minimum difference from the average value of the RR intervals.

**Table 1** Baseline Clinical Characteristics of the Patients With Long-Lasting Atrial Fibrillation

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>M/F</th>
<th>Duration of AF (months)</th>
<th>Underlying heart disease</th>
<th>LA diameter (mm)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n=8)</td>
<td>60±10</td>
<td>4/4</td>
<td>Mean</td>
<td>16±2</td>
<td>46±24.5</td>
</tr>
<tr>
<td>Group II (n=8)</td>
<td>60±11</td>
<td>7/1</td>
<td>Median (range)</td>
<td>29±29</td>
<td>43.8±5.8</td>
</tr>
<tr>
<td>Group III (n=7)</td>
<td>57±10</td>
<td>6/1</td>
<td>Underlying heart disease</td>
<td>101±91*</td>
<td>46.4±5.0</td>
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<tr>
<td>Valvular disease</td>
<td>5</td>
<td>2</td>
<td>Congenital disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1</td>
<td>1</td>
<td>Hypertension</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>1</td>
<td>LA diameter (mm)</td>
<td>46.0±4.5</td>
<td>43.8±5.8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66±8</td>
<td>65±13</td>
<td>59±10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise indicated. AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction. *p<0.05 vs Group I and II.

**Statistical Analysis**
All data are expressed as mean ± SD. Paired and unpaired t-tests were used for comparison between the 2 groups of results. Comparison among 3 groups of data was performed by an ANOVA with multiple comparisons made by Bonferroni’s test. Comparison of serial measures was obtained by repeated measures ANOVA coupled with the Student-Newman-Keuls test. Results were considered to be statistically significant at p<0.05. All statistical analyses were performed with the Statview for Windows program.

**Fig 1.** Power spectral analysis of the fibrillation waves. The fibrillation cycle length (FCL) was calculated from the peak frequency with the maximum magnitude from each epoch. The fibrillation organization index (FOI) was derived from the area ratio of the spectral zone with the maximum power to the total spectral area from 3 to 12 Hz from each epoch.
Results

Conversion to SR by Bepridil and Aprindine

In 8 of 23 patients, bepridil converted AF to SR 20 days (7–42 days) after the drug had been started (Group I). Fifteen patients who initially had failed to respond to bepridil and did not have abnormal prolongation of the QT interval received oral aprindine in addition to bepridil, and in 8 of them AF was terminated 19 days (7–28 days) later (Group II). Group III consisted of the remaining 7 patients who failed to convert to SR despite combination therapy. The final success rate of conversion with bepridil alone or in combination with aprindine was 70% (16 of 23 patients). The baseline clinical characteristics are presented in Table 1. The duration of AF was longer in Group III than in the other 2 groups. LVEF and left atrial dimension (LAD)
Effects of Bepridil and Aprindine on Fibrillation Wave Characteristics

Representative ECGs and spectral analyses from a case of AF termination by the combination of bepridil and aprindine are shown in Figs 2 and 3. Changes in FCL and FOI by bepridil alone or the combination of bepridil and aprindine are summarized in Fig 4. Bepridil increased both FCL (from 152±22 to 204±28 ms, p<0.001) and FOI (from 38.0±3.9 to 47.4±7.0%, p<0.01) in Group I. Bepridil increased FCL (from 142±14 to 175±27 ms, p<0.001), but did not change FOI (from 39.0±4.8 to 39.0±2.2%). The addition of aprindine to bepridil increased both FCL and FOI, and terminated AF. Bepridil increased both FCL and FOI by the combination of bepridil and aprindine remained smaller, and AF did not convert to sinus rhythm. FCL: *p<0.01 and **p<0.001 vs control. FOI: †p<0.05 and ††p<0.01 vs control.

Drug-Induced Changes in FCL and FOI for Chemical Cardioversion of Persistent AF

The occurrence of pharmacological conversion was significantly higher in patients with FCL ≥190 ms or FOI ≥45% after drug administration. Conversion occurred in 100% patients with both FCL ≥190 ms and FOI ≥45% and in 0% of those with both FCL <190 ms and FOI <45% (Fig 6). Patients with either a combination of FCL ≥190 ms and FOI <45% or FCL <190 ms and FOI ≥45% achieved conversion in 9 of 16 (56%) episodes of persistent AF.
Effects of Bepridil and Aprindine on the QT Interval

After bepridil treatment the QTc increased from 0.41±0.04 to 0.46±0.03 s in Group I, from 0.38±0.04 to 0.41±0.03 s in Group II, and 0.40±0.03 to 0.43±0.03 s in Group III. The increase in QTc with bepridil alone did not differ among the 3 groups and the addition of aprindine did not change the QTc in either Group II (to 0.42±0.02 s) or Group III (to 0.44±0.05 s). However, the bepridil dosage was reduced from 200 mg/day to 100 mg/day in 1 patient of Group II because of excessive QT prolongation (QTc 0.52 s) after conversion to SR. No other adverse effects, including liver injury, necessitating drug discontinuation occurred.

Discussion

The present study demonstrated that bepridil terminated persistent AF together with a significant increase in both FCL and FOI. After the addition of aprindine to bepridil, AF could be terminated when both FCL and FOI were more increased. When the increase in FCL and FOI was less, even after the combination of bepridil and aprindine, AF persisted. These results suggest that an increase in both FCL and FOI provides important information related to the termination of long-lasting persistent AF by bepridil alone or in combination with aprindine. Drug-induced changes in FCL and FOI are helpful in predicting chemical cardioversion of persistent AF.

Termination of Persistent AF With Respect to Fibrillation Wave Characteristics

During AF, manual measurements of FCL are difficult and inaccurate and several investigators have proposed using spectral analysis as a new method for noninvasive assessment of FCL in humans.2-4 They analyzed the frequency characteristics of fibrillation waves from surface ECG using QRST subtraction methods and confirmed that spectral analysis of surface ECG could be useful for the quantification of FCL. Bollmann et al reported that FCL was an accurate predictor of conversion of paroxysmal AF with a class III antiarrhythmic drug, ibutilide.13 In our previous study, the mean FCL at the right atrial free wall was a good predictor of termination of paroxysmal AF with class I antiarrhythmic drugs.5

In the present study, spectral analysis was introduced not only for measuring FCL but also for quantifying AF organization. The ratio of the area of the zone with the maximum power to the total area between 3 and 12 Hz, which may represent the degree of AF organization, was calculated from the surface ECG (Fig 1) and termed the FOI. The FCL consists of a refractory period and temporal excitable gap, whereas the FOI is related to the spatial size of the reentry circuit (pathway length), consisting of the wavelength and spatial excitable gap. We analyzed the serial changes of these indices before and after drug administration. A critical increase in both FCL and FOI was required for bepridil alone or in combination with aprindine to terminate long-lasting persistent AF (Fig 6). In patients who are scheduled for termination of persistent AF, a combination of the FCL and FOI after drug administration may become a useful indicator of the success of chemical cardioversion. If the patient shows a smaller increase in FCL and FOI after bepridil, the addition of aprindine is recommended. If the patient still shows a small increases in FCL and FOI after the combination of bepridil and aprindine, chemical cardioversion should be abandoned.

Mechanism of Termination of Persistent AF

In vagally induced canine AF, nifekarant (a class III antiarrhythmic drug) terminated AF in association with increases in both FCL and wavelength, whereas pilsicainide (a class Ic drug) terminated AF without an increase in wavelength.16 Wijffels et al measured wavelength using activation maps and found increases in both FCL and excitability gap, and unchanged wavelength, before termination of AF by class I or III drugs.17 Recently, Kawase et al demonstrated a widening of the excitable gap related to an increase in core diameter of acetylcholine-induced canine AF with class Ic drug, pilsicainide.18

Long-lasting AF induces both electrical and structural remodeling, and it is the atrial remodeling in persistent AF that makes chemical conversion more difficult than in paroxysmal AF. Persistent AF changes the properties of the ion channels of atrial cells, such as decreasing protein levels for the L-type Ca channel and several K channels (Kv4.3, Kv1.5, HERG, mink, and Kir3.1).19 In a canine model of AF with atrial tachypacing, amiodarone preserved down-regulation of the L-type Ca channel and reversed pacing-induced shortening of atrial refractoriness.20 It is possible that bepridil may reverse some of these remodeled channels and change the fibrillation wave characteristics in the same way as amiodarone. In the present study, the increase in FCL by bepridil alone may be attributable mainly to the action of a class III antiarrhythmic drug increasing atrial refractoriness, and the combination with aprindine may cause conduction delay at pivotal points of functional reentry, thus further increasing the FCL. These effects may lead to prolongation of FCL with fewer wavelets and increase the possibility of eliminating all circulating wavelets simultaneously.

Power spectra showing multiple peaks and lower FOI may represent a greater number of circulating wavelets in the atria as compared with those with single peak pattern. Everett et al21 quantified AF organization using spectral analysis in a canine AF model and demonstrated that the defibrillation energy of AF was dependent on the degree of

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AF organization; more defibrillation energy was required for the less organized fibrillation waves. According to the multiple wavelets hypothesis, the number of wavelets varies as a result of the variation in the rate of wavelet formation and extinction. Drugs decreasing the number of wavelets may increase the FOI and thereby increase the possibility of terminating AF. These observations suggest that termination of AF may be dependent on the organization of the wavelets as well as on an increase in the circulating interval of the wavelets; in other words, the FCL.

Electrophysiology of Bepridil and Aprindine

Bepridil, a multi-channel blocker, prolongs the duration of the atrial action potential and is expected to be effective for the conversion of AF. However, it also prolongs the QT interval, resulting in a possible risk for torsades de pointes. In a previous study, bepridil (200–600 mg/day) was associated with the development of serious ventricular arrhythmias caused by excessive prolongation of the QT interval. In the present study, however, the dosage of bepridil was 200 mg/day and serum K ≥ 3.8 mmol/L was maintained by administration of either an angiotensin-converting enzyme inhibitor or spironolactone to avoid the proarrhythmic effects of bepridil.

The addition of oral aprindine, a class Ib antiarrhythmic drug, to bepridil enhanced the rate of AF termination. We selected aprindine as the additional drug because of its unique channel blocking properties. Aprindine blocks the Na channel, mainly when the channel is in the inactive state, as an intermediate kinetic drug. Bepridil would enhance the Na-channel blocking effect of aprindine because bepridil prolongs both the action potential duration and the duration of the inactivated state of the Na channel in the atrium. The enhanced Na-channel blocking effect of aprindine may increase post-repolarization refractoriness, thereby contributing to both the organization of the fibrillation wave and the prolongation of FCL. However, frequency-dependent atrial conduction velocity was not evaluated in the present study and in ventricular muscle treated with aprindine, the addition of lidocaine decreased the use-dependent block and increased Vmax. Further studies concerning the Na-channel blocking effects of the combination with bepridil and aprindine are needed. In addition to the action of class I antiarrhythmic drugs, aprindine moderately reduces both the delayed rectifier K current and the hyperpolarization-activated inward current. However, the precise mechanism of the accentuated organization of the fibrillation waves by the combination of aprindine and bepridil is unclear.

Conclusion

The present study indicates that a critical increase in both FCL and FOI might be important for the chemical termination of persistent AF. Because neither FCL nor FOI before drug administration differed between the responders (Group I and II) and non-responders (Group III), the mechanisms of the different responses of FCL and FOI to bepridil and aprindine remain unclear. Differences in the plasma concentrations of bepridil and aprindine, the electrophysiological and anatomical characteristics of the atria, and other factors might contribute to the different responses observed in the present study. Further studies are needed to clarify these issues using a larger number of patients with different underlying atrial electrophysiological backgrounds of AF.

References

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