Pharmacological Cardioversion of Persistent Atrial Fibrillation With and Without a History of Drug-Resistant Paroxysmal Atrial Fibrillation

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Background  Suppression by antiarrhythmic drugs of the maintenance mechanisms could convert persistent atrial fibrillation (AF) to sinus rhythm (SR). Whether a history of drug-resistant paroxysmal AF (PAF) would affect the outcome of pharmacological conversion of persistent AF by bepridil or in combination with aprindine was evaluated in the present study.

Methods and Results  The study group comprised 51 consecutive patients (24 men, 61±8 years) undergoing pharmacological conversion of persistent AF lasting >1 month. Drug-resistant PAF was defined as AF and at least 2 ineffective antiarrhythmic drugs for suppression of AF recurrence. Fast Fourier transform analysis of fibrillation waves was used to measure fibrillation cycle length (FCL) from the peak frequency. Fifteen patients had a history of drug-resistant PAF (Group I), and the remaining 36 did not (Group II) before diagnosis of persistent AF. Ten patients (67%) in Group I and 26 patients (72%) in Group II were restored to SR by bepridil alone or in combination with aprindine after 29±15 days of drug administration. Before conversion to SR, bepridil increased the FCL more in Group II than in Group I. During a 12-month follow-up period, 4 of 10 patients in Group I and 2 of 26 patients in Group II (p<0.01) had recurrence of persistent AF with bepridil alone or in combination with aprindine.

Conclusions  A history of drug-resistant PAF does not affect the efficacy of pharmacological conversion by bepridil or in combination with aprindine. However, recurrence of AF was significantly higher in patients with such a history.  (Circ J 2006; 70: 1138–1141)

Key Words: Antiarrhythmic drug; Aprindine; Atrial fibrillation; Bepridil; Defibrillation

Pharmacological termination of atrial fibrillation (AF) lasting more than 1 week is usually considered difficult, but we have demonstrated that oral administration of bepridil alone or in combination with aprindine can restore sinus rhythm (SR) in nearly 70% patients with long-lasting persistent AF (AF >1 month), because bepridil suppresses the mechanisms of maintaining persistent AF.

Some cases of persistent AF may be preceded by episodes of paroxysmal AF (PAF). If the mechanisms that initiate PAF are resistant to antiarrhythmic drug therapy, pharmacological cardioversion of persistent AF would be difficult because of the presence of a drug-resistant substrate for AF. However, whether a history of drug-resistant PAF would affect the outcome of pharmacological conversion is unclear, so we compared the efficacy of pharmacological cardioversion in patients with long-lasting persistent AF with and without a history of drug-resistant PAF.

Methods

Subjects  All 51 patients had at least 1 month and were referred to Toyama University Hospital for elective cardioversion of AF between April 2003 and December 2005. Duration of AF was quantified with ECG recordings, and the median was 12 months (range 1–168 months). All patients underwent physical examination, 12-lead ECG, echocardiography, and biochemical and hematological testing. Excluded were women of child-bearing age and patients with myocardial infarction or revascularization within 3 months, left ventricular ejection fraction <0.35, QTc >0.46 s, serum K <3.8 mmol/L, or a history of sick sinus syndrome. Anticoagulation therapy with warfarin (international normalized ratio =2.0) had been given to all patients for at least 3 weeks before pharmacological conversion was attempted. Concurrent control of the ventricular rate with calcium antagonists or β-blocking drugs was permitted. All patients gave their written informed consent to inclusion in the study. The protocol was approved by the hospital Ethics Committee.

Study Protocol  Patients were divided into 2 groups; Group I consisted of patients with persistent AF that had been preceded by episodes of drug-resistant PAF, and Group II consisted of patients who had no history of drug-resistant AF before
diagnosis of persistent AF. Drug-resistant PAF was arbitrarily defined at least 2 ineffective antiarrhythmic drugs in suppressing AF recurrence.

The details of the pharmacological conversion protocol have been published previously.2 Briefly, after giving information about the risks and benefits of bepridil and aprindine therapy for AF termination, patients received oral bepridil (200 mg/day) and were followed for 2–4 weeks. If bepridil failed to restore SR and the QTc interval was not prolonged markedly, oral aprindine (40 or 60 mg/day) was added to bepridil and the patients were followed for another 4 weeks. After pharmacological conversion, the treatment was continued at the same dosage unless marked QT prolongation (QTc >0.50 or >25% increase) or sinus bradycardia occurred. During SR and AF, the QT interval was corrected by dividing the measured QT interval by the square root of the preceding RR interval that showed the minimal difference between the average values of RR intervals (QTc).

**Fibrillation Wave Analysis**

Spectral analyses of the fibrillation waves were performed before conversion to SR in both groups as in our previous study. Surface ECG lead V1 was digitally stored on-line on a microcomputer (Value Star NX, NEC, Tokyo, Japan), and the QRST complexes were subtracted using a template-matching algorithm. ECG-segments were digitized at a sampling rate of 1 kHz. Frequency analysis of the subtracted electrograms involved 3 steps: (1) bandpass filtering, (2) application of a Hamming window and (3) 4,096-point fast Fourier transformation. A 50% overlap of adjacent spectral analyses allowed the use of averages of 20 epochs of analyses within a single 44-s data set. 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 (in ms = 1,000 /frequency), named as fibrillation cycle length (FCL), and averaged from 20 epochs.

**Table 1  Baseline Clinical Characteristics of the Patients With AF**

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=15)</th>
<th>Group II (n=36)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>61.5±11.4</td>
<td>60.9±10.3</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/6</td>
<td>26/10</td>
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<tr>
<td>Duration of AF (months)</td>
<td>Mean 46.7±48.0</td>
<td>33.7±50.1</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>36 (2–168)</td>
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<tr>
<td>Underlying heart disease</td>
<td>Valvular disease</td>
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<tr>
<td></td>
<td>Congenital disease</td>
<td>0</td>
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<tr>
<td></td>
<td>HCM</td>
<td>1</td>
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<tr>
<td></td>
<td>Hypertension</td>
<td>6</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>LA diameter (mm)</td>
<td>43.8±5.5</td>
<td>44.0±7.9</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.61±0.10</td>
<td>0.65±0.10</td>
</tr>
</tbody>
</table>

Data are mean±SD, unless otherwise indicated.

AF, atrial fibrillation; Group I, patients with a history of drug-resistant paroxysmal AF; Group II, patients without a history of drug-resistant paroxysmal AF; HCM, hypertrophic cardiomyopathy; LA, left atrium; LVEF, left ventricular ejection fraction.

**Fig 1.** ECGs and spectral analyses of fibrillation waves in a representative patient with conversion of atrial fibrillation (AF) by bepridil and aprindine. This 61-year-old male had persistent AF lasting 36 months preceded by drug-resistant paroxysmal AF (18 months). He had apical type of hypertrophic cardiomyopathy and enlarged left atrium (48 mm). Before bepridil administration QTc was 0.44 and fine fibrillation waves were observed in V1. After a combination of bepridil and aprindine QTc was 0.43, and fibrillation waves became coarser in V1. After 30 days of bepridil therapy sinus rhythm was restored. During sinus rhythm QTc was 0.44. Mean fibrillation cycle length (FCL) calculated from the peak frequency was 141 ms before bepridil (Right-upper) and increased to 207 ms after bepridil and aprindine therapy (Right-lower). The peak frequency shifted to the left after a combination of bepridil and aprindine had been started.
and Wilcoxon tests were used for comparison of the 2 groups of results. Univariate analyses using chi-square tests evaluated categorical data. A Kaplan-Meier analysis with the log-rank test was used to compare the probability of freedom from recurrence of AF. Results were considered to be statistically significant at p<0.05. All statistical analyses were performed with the Statview for Windows program (Abacus Concepts, Berkeley, CA, USA).

**Results**

**Baseline Characteristics**

Group I comprised 15 patients and Group II had 36 patients. In Group I, antiarrhythmic drugs administered before transition to persistent AF were flecainide in 11, cibenzoline in 10, disopyramide in 8 and pirmenol in 1. Duration of persistent AF and echocardiographic variables were not different between the groups (Table 1).

**Conversion to SR**

A representative patient is shown in Fig 1. Ten patients (67%) in Group I and 26 (72%) in Group II had SR restored pharmacologically (Fig 2). In Group I, SR was restored by bepridil alone in 2 patients and a combination of bepridil and aprindine in 8 patients after 27±14 days of bepridil administration. In Group II 15 patients had SR restored by bepridil alone, and the remaining 11 patients by a combination of bepridil and aprindine after 30±15 days of bepridil administration. The proportion of patients restored to SR with bepridil alone was significantly greater in Group II than in Group I (p<0.05). Before bepridil administration, the FCL did not differ between Group I (140±14 ms) and Group II (152±26 ms). Bepridil increased the FCL more in Group II (196±38 ms) than in Group I (166±13 ms, p<0.05).

During a 12-month follow-up period, 4 of 10 patients in Group I and 2 of 26 patients in Group II had recurrence of persistent AF (Figs 2, 3). The maintenance of SR was achieved more frequently in Group II than in Group I (p<0.01). After restoration of SR, the QTc interval increased to 0.46±0.04 s or by 18±14%. No adverse effects necessitating drug discontinuation occurred, apart from 1 patient who discontinued bepridil administration because of marked QTc prolongation (0.60 s) after restoration of SR.

**Discussion**

Of 51 patients with long-lasting persistent AF, 15 had had preceding drug-resistant PAF. Pharmacological conversion with bepridil alone or in combination with aprindine was achieved in 67% of patients with a history of drug-refractory AF and SR could be maintained in 60% of converters after a 12-month follow-up. A history of drug-resistant recurrent PAF did not affect pharmacological conversion after it became persistent. However, maintenance of SR over the 12-month period was significantly lower in patients with a history of drug-resistant PAF than in those without.

In the present study, we focused on a history of drug-refractory PAF in patients with established persistent AF. We did not find a history of recurrent PAF as a prelude in two-thirds of the patients with persistent AF. Because patients in Group II had not been treated with antiarrhythmic drugs for SR restoration before the diagnosis of persistent AF, it is possible that the group included patients who had a drug-resistant substrate for PAF. Patients with mitral stenosis who have a larger left atrium, for instance, usually maintain SR until they have triggering events of AF. Once the initiating premature atrial beats appear, induced AF has a tendency not to terminate spontaneously because of the
presence of an established substrate for maintenance of AF. This could lead to an absence of recurrent episodes of PAF before the diagnosis of persistent AF in Group II.

In patients with frequent episodes of PAF, atrial electrical remodeling is associated with marked shortening of the action potential duration (APD) and loss of rate adaptation of the APD, leading to shortening of the FCL. A shortened FCL will favor transition from paroxysmal to persistent AF, which is the final common pathway, irrespective of various initiating mechanisms of AF. After bepridil administration, the patients in Group I had a shorter FCL than those in Group II and as shown in Fig 1, they needed a combination of bepridil and aprindine more frequently for pharmacological conversion, probably because they had a drug-resistant substrate for AF.

Generally, patients with persistent AF who had a history of drug-refractory PAF attempt pharmacological conversion once and then accept rate-control therapy. In the present study, patients with a history of drug-resistant AF had almost the same pharmacological conversion rate as those without a history. Hence, pharmacological restoration of SR could become a therapeutic option for patients with persistent AF irrespective of a history of drug-refractory PAF. Bepridil is a class IV antiarrhythmic drug, but it has strong class III activity and careful observation is necessary to prevent excessive QT prolongation and torsades de pointes. Aprindine is classified as a class Ib drug and is expected not to prolong the QT interval; however, the response of the QT interval to the additional administration of aprindine is variable and should be monitored carefully.

**Study Limitations**

First, not all patients had antiarrhythmic drug therapy before they were established as having persistent AF and it is possible that some patients in Group II had drug-resistant PAF. From the clinical viewpoint, we arbitrarily classified patients according to the presence of a history of drug-resistant PAF. Second, patients with preserved left ventricular ejection fraction >0.35 were included. Persistent AF with a history of drug-resistant PAF in patients with left ventricular dysfunction might have responded differently. Further studies are needed to clarify clinical efficacy and the safety of bepridil and aprindine in such patients. Third, although patients with persistent AF preceded by drug-refractory AF had SR restored pharmacologically, recurrence of persistent AF occurred in 40% of them during the 12-month follow-up period. Additional treatment for initiation mechanisms may be needed.

**Conclusions**

The present study revealed the usefulness of pharmacological cardioversion using bepridil alone or in combination with aprindine in cases of persistent AF with and without a history of drug-resistant PAF. However, recurrence of AF was higher in patients with such a history.

**References**