Conversion and Maintenance of Sinus Rhythm by Bepridil in Patients With Persistent Atrial Fibrillation

Yuji Nakazato, MD; Masayuki Yasuda, MD; Akitoshi Sasaki, MD; Youji Iida, MD; Yasunobu Kawano, MD; Kaoru Nakazato, MD; Takashi Tokano, MD; Yoriaki Mineda, MD*; Masataka Sumiyoshi, MD*; Yasuro Nakata, MD*; Hiroyuki Daida, MD

Background Bepridil has multiple ion-channel blocking effects similar to amiodarone and is expected to have anti-arrhythmic effects that are useful for the management of atrial fibrillation (AF). The aim of this study was to clarify the conversion of persistent AF and maintenance of sinus rhythm (SR) by oral bepridil.

Methods and Results Oral bepridil was administered to 112 patients (83 males, 29 females; age: 59.0±10.8 years) with persistent AF lasting an average of 5 months. The conversion effects and maintenance of SR after pharmacological or direct current (DC) cardioversion, as well as the incidence of adverse complications, were evaluated. In 65 of 112 (58%) patients, SR was restored within 6 months (average: 2.1 months) following bepridil administration. DC cardioversion was carried out for 21 of the remaining 47 patients with unsuccessful pharmacological conversion, and all had restoration of SR. Eventually, of the 86 patients in total who were restored to SR by either bepridil or DC cardioversion, 70 (81%) patients maintained SR after a mean follow-up of 18 months. No serious adverse complications were observed, except for marked QT prolongation in 2 cases.

Conclusion Bepridil showed favorable conversion effects in patients with persistent AF and was highly effective for maintaining SR after pharmacological or electrical cardioversion. However, careful follow-up is necessary for the prevention of torsade de pointes caused by QT prolongation.

Key Words: Atrial fibrillation; Bepridil; Cardioversion

Bepridil hydrochloride was originally developed as an anti-anginal drug with calcium channel blocking effects, but it is also known to have sodium and potassium channel blocking actions.1–4 Therefore, bepridil is expected to have anti-arrhythmic effects, similar to those of class III drugs such as amiodarone, that would be useful for the management of atrial fibrillation (AF).5–7 However, despite the clinical efficacy of bepridil, previous reports have emphasized the risk of torsade de pointes (TdP) because of QT prolongation from its relatively strong potassium channel blocking action.8 There have only been a few studies of the clinical efficacy of bepridil, and those have particularly focused on the treatment of persistent AF.8,9 Therefore, we investigated the efficacy of oral bepridil for converting persistent AF and then maintaining sinus rhythm (SR).

Methods

Bepridil was administered to 112 patients (83 males, 29 females; average age, 59.0±10.8 years; range, 19–81 years) with persistent AF. In this study, persistent AF was defined as non-self-terminating AF lasting more than 48 h and requiring pharmacological or electrical conversion to restore sinus rhythm, in accordance with previous reports.10 However, the AF duration in the majority of patients in this study ranged from 1 to 24 months (mean, 4.7 months). Underlying heart disease was observed in 70 patients: hypertension (37), ischemic heart disease (12), mitral valve disease (10), aortic valve disease (3), hypertrophic cardiomyopathy (2), dilated cardiomyopathy (2), chronic myocarditis (2), sick sinus syndrome (1) and chronic obstructive lung disease (1). The remaining 42 patients had no obvious underlying heart disease. All the patients underwent echocardiography for evaluation of their cardiac function before the treatment. The mean left ventricular ejection fraction (LVEF) was 64±11% and left atrial dimension

Table 1 Characteristics of the Patients With Persistent Atrial Fibrillation (n=112)

<table>
<thead>
<tr>
<th>Age (years, range)</th>
<th>59±10.8, 19–81</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>83/29</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>42</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>12</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>10</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>3</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>2</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>2</td>
</tr>
<tr>
<td>Chronic myocarditis</td>
<td>2</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1</td>
</tr>
<tr>
<td>Echocardiography parameters</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>64±11</td>
</tr>
<tr>
<td>LAd (mm)</td>
<td>40±6</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>5.2, 1–24</td>
</tr>
<tr>
<td>Average, range</td>
<td></td>
</tr>
</tbody>
</table>

EF, ejection fraction; LAd, left atrial dimension; AF, atrial fibrillation.
Bepridil for Persistent AF

(LAd) was 40±6 mm. Class Ia or Ic drugs were refractory in 56 patients who had been administered an average of 2 types of drugs (range, 1–5). In the remaining 56 patients, bepridil was used as the initial drug. After informed consent was obtained, bepridil was administered daily in the range of 100–200 mg according to age, gender, renal function and body weight. If SR was restored, the treatment was maintained unless obvious adverse complications were noted. In patients not receiving anti-coagulation therapy, warfarin was concurrently started to prevent thromboembolic complications. Digitalis, β-blockers or calcium antagonists were used concomitantly for rate control if required. The exclusion criteria were: (1) AF ≥2 years, (2) LAd >50 mm, (3) LVEF <40%, (4) history of more than 2 electrical cardioversions, or (5) QT interval >0.5 s on baseline ECG. The characteristics of the patients are shown in Table 1.

Pharmacological conversion and subsequent maintenance of SR after administration of bepridil were evaluated. If SR was not restored after 3 months of observation, in principle, a direct current (DC) cardioversion was scheduled. For patients who refused DC cardioversion, bepridil was continued with the expectation that the sinus conversion effect was delayed. The patients who had SR restored after 3 months were included in the responder group for pharmacological conversion by bepridil. ECG parameters including heart rate, QRS width, QT interval and QTc were measured before and after bepridil administration. The incidence of adverse complications was also evaluated from subjective symptoms and the ECG recordings at 1 week, 2 weeks, monthly until 6 months and then every 3 months. An ambulatory ECG was recorded at 1 month and then every 3 months after administration of bepridil.

Statistical Analysis

The results are presented as the mean±SD. Differences between responders and non-responders were compared using an unpaired t-test and significance was set at p<0.05. The chi-square test was performed if appropriate.

Fig 1. Clinical efficacy of bepridil. In 112 patients with persistent atrial fibrillation, 65 (58%) were converted to sinus rhythm (SR) by bepridil. Of the remaining 47 patients, DC cardioversion resulted in successful conversion to SR in 21 patients. Finally, 70 patients were maintained in SR during a mean follow-up of 18 months.

Fig 2. Mean time to conversion to sinus rhythm after administration of bepridil (2.1 months).
The outcomes of this study are presented in Fig 1. In 65 of 112 (58%) patients, SR was restored with a mean conversion time of 2.1 months. In the majority of these patients, SR was restored within 6 months following administration of bepridil (Fig 2) and these patients were defined as bepridil responders. Although AF recurred in 8 patients, 57 of the 65 (89%) patients maintained SR for an average follow-up of 12 months (range: 0.5–43.7 months). Of the remaining 47 patients with unsuccessful pharmacological conversion to SR, 21 underwent DC cardioversion, which restored SR in all of them and 13 (62%) maintained SR during an average follow-up period of 14 months (range, 3.3–25.5 months). As a result, 86 patients in total had SR restored by bepridil or DC cardioversion, and 70 (81%) maintained SR with an average follow-up period of 18 months (Fig 3). The remaining 42 patients who failed to convert to SR were managed by rate control therapy. There were no significant differences in age, gender, underlying disease, LVEF or LAd, AF duration, or the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) between the bepridil responders and non-responders (Table 2).

Regarding the ECG parameters, the heart rate decreased from 68.2±11.0 to 60.6±9.0 beats/min (p<0.01), and the

**Results**

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TQT interval was prolonged from 0.38±0.03 to 0.42±0.05 s. The QRS width remained unchanged (0.09±0.02 to 0.09±0.02 s), and QTc was slightly prolonged (0.43±0.03 to 0.44±0.03) without statistical significance. The ECG of patients who had SR restored by bepridil commonly demonstrated morphological changes in their fibrillatory waves; that is, the fibrillation waves were initially fine and of low amplitude, but gradually became larger and more organized (similar to atrial flutter) just before the restoration of SR (Fig 4).

Regarding adverse complications, 1 patient was easily fatigued and 1 had dizziness, but in both cases these symptoms subsided after cessation of bepridil. Sinus bradycardia was observed in 3 patients. We discontinued bepridil in 1 of these patients, but the remaining 2 continued on bepridil at a lower dose. QT prolongation was observed in 8 patients. Although TdP was not observed, 2 patients showed marked QT prolongation (>0.60 s), and bepridil was therefore discontinued.

**Discussion**

The main findings of this study are that 58% of the patients (65/112) with persistent AF were converted to SR after administration of bepridil with a mean conversion time of 2.1 months, SR was maintained over a mean follow-up of 18 months in 81% of the patients (70/86) who were successfully converted by bepridil or DC cardioversion, and there were no serious adverse complications, such as TdP, other than 2 cases of marked QT prolongation.

**SR Conversion Effect**

In persistent AF, spontaneous SR conversion is unlikely, and pharmacological or electrical cardioversion is generally scheduled under appropriate anti-coagulation therapy. Regarding pharmacological cardioversion, class Ia, Ic and III drugs are the drugs of choice, but their efficacy may decline in long-lasting persistent AF. Bepridil was originally developed as an anti-anginal drug, but also has multiple ion-channel blocking effects, including sodium, potassium and calcium channels.1–4 In particular, its potassium channel blocking effect is a characteristic feature. The action potential duration prolongs the action potential duration, and it is therefore expected to have anti-arrhythmic effects for AF, similar to those of amiodarone.1 Yoshida et al compared the efficacies of class Ic drugs and bepridil for preventing paroxysmal AF, and observed that the main effect of bepridil was a class III anti-arrhythmic action because of its effectiveness on paroxysmal AF with relatively short f-f intervals (small excitable-gap).6,7 Fujiuki et al used spectral analysis to compare the interval of the fibrillation cycle length (FCL) before and after bepridil and they noted a greater increase in FCL in responders and that the fibrillation waves became coarser before termination.8 Although we did not analyze the fibrillation waves precisely in the current study, a representative ECG of the responders demonstrated that the fibrillatory waves were initially small and fine and then exhibited a coarse and large morphology prior to sinus restoration, consistent with the observations of Fujiuki et al.9

Perelman et al reported a comparison of the effects of amiodarone and bepridil in 14 patients with AF.10 The conversion rate to SR was 4 of 10 (40%) patients by amiodarone and 9 of 14 (64%) patients by bepridil. Although the number of patients was relatively small, Fujiuki et al9 observed that bepridil restored SR alone or in combination with aprindine in 22 of 32 (69%) patients with persistent AF. In the present study, the conversion rate to SR was 65 of 112 (58%) patients and therefore comparable to their results.

According to recent basic studies, bepridil blocks the slow components of multiple K+ currents.12,13 In acute perfusion experiments, the ultra rapid (Ik-ur) K+ current was also specifically blocked by bepridil, but not by amiodarone.11 Although it is difficult to directly apply these experimental results to the clinical setting, the difference in effectiveness for atrial tachyarrhythmia suppression between bepridil and amiodarone may be explained by the Ik-ur blocking effect, because this channel only exists in the atrium. In their mathematical model of human atrial action potentials, Courtemanche et al noted that the combined inhibition of Ik and Ik-ur is synergistic and produces a greater prolongation of the action potential than the sum of the effects of individual channel blockade,14 which is an additional explanation for the superior efficacy of bepridil over amiodarone.

Regarding the time to sinus conversion, the mean interval was 2.1 months in this study. Kochiadakis et al observed that amiodarone was relatively slow in producing successful conversion, ranging from 9 days to 1 month.15 Perelman et al reported that the estimated time to conversion was less than 3 weeks with bepridil, but 1–4 months with amiodarone.16 In the present study, bepridil required a much longer time to convert AF to SR, namely a mean interval of 2.1 months. Although the precise mechanism for the late conversion remains unclear, 3 possible mechanisms can be considered. The first is that bepridil has a relatively slow onset of action and therefore takes longer to achieve a steady-state. The second is that the average time to conversion included the cases that were restored to SR after 3 months. The third was suggested by recent basic research demonstrating the ionic changes in atrial remodeling. The L-type Ca2+ blocker, verapamil, was found to prevent short-term rapid pacing-induced shortening of the atrial effective refractory period.16,17 and T-type Ca2+ blockers were found to work particularly well in preventing such effects in the mid to late phases of atrial remodeling compared with L-type blockers.18 Bepridil has a T-type Ca2+ channel blocking effect as well as an L-type Ca2+ channel blocking effect, and therefore the reverse-remodeling effect in the mid to late phases may represent one of the mechanisms for the delayed conversion to SR.

Regarding factors that influence the conversion to SR, Kochiadakis et al pointed out that AF duration and LAd were independent predictors of conversion.15 A comparison of the bepridil responders and non-responders in this study revealed no significant differences in various factors between the 2 groups.

**SR Maintenance**

Regarding the efficacy of SR maintenance by bepridil, clinical follow-up data are scarce. According to a prospective multicenter trial, after a mean follow-up of 16 months, AF recurred in 71 of 201 (35%) patients using amiodarone and 127 of 201 (63%) patients using sotalol or propafenone.19 In other words, SR was maintained in, at most, 65% of patients, even with amiodarone, and the remaining patients would probably experience recurrence of AF during the follow-up. In the present study, SR was maintained in 70 of 86 (81%) patients restored by bepridil or DC cardioversion during an average follow-up of 18 months.
and therefore it seems to have a comparable or superior effect to that of amiodarone for maintaining SR. In a more recent study, Yamashita et al demonstrated an increase in the mRNA level of the Kv1.5 channel within a few hours after rapid-atrial pacing in the rat heart. Kobayashi et al reported that bepridil inhibits the human Kv1.5 channel current related to Ikur, and may therefore be useful for preventing the recurrence of paroxysmal AF. The mechanism of SR maintenance is still unclear, but it is considered that bepridil may prevent the short-term remodeling effect in the atrium as well as the reversed effect in mid- to long-term remodeling as previously described.

Adverse Complications
Despite the efficacy of bepridil on AF, previous reports have warned that the relatively strong potassium channel blocking effect often causes unfavorable adverse complications, such as TdP caused by QT prolongation. Perelman et al. reported that the relatively strong potassium channel blocking effect often causes unfavorable adverse complications, such as TdP caused by QT prolongation. Perelman et al concluded that the risks outweigh the benefits because of the high rate of ventricular arrhythmias such as TdP. However, their dose of bepridil was 200–600 mg/day and it may have been this relatively higher dosage that was the cause of the higher incidence of serious ventricular arrhythmias. We consider that an appropriate dose of bepridil is a maximum of 200 mg/day and we performed careful follow-up including observation of the QT interval and serum potassium concentrations. This dosage resulted in no serious complications, other than 2 cases of marked QT prolongation in which we ceased bepridil administration. However, we should always bear the risk of TdP in mind, and careful observation is necessary.

Study Limitations
This study was performed in a non-randomized fashion without controls and in a retrospective manner, and therefore sampling bias could not be eliminated. The study population contained patients with varying durations of persistent AF, and it was difficult to judge the precise date of onset of the AF, particularly in the asymptomatic patients. However, AF lasted at least 1 month or longer in most of the patients in this study and it may be acceptable to state that bepridil showed relatively high conversion rates to SR in patients with persistent AF. Another limitation is the relatively short follow-up period after sinusrhythm conversion. To confirm the long-term efficacy of sinus maintenance by bepridil, a much longer follow-up period is required. A prospective randomized-control study is necessary to verify the clinical efficacy of bepridil for persistent AF.

Conclusion
Bepridil showed favorable rates of AF conversion and sinus maintenance after pharmacological or DC cardioversion. Bepridil is a clinically safe and useful drug for persistent AF. However, careful observation of the QT interval should always be done.

References