Use of Bepridil in Combination With Ic Antiarrhythmic Agent in Converting Persistent Atrial Fibrillation to Sinus Rhythm

Shinobu Imai, MD; Fumio Saito, MD; Hidehito Takase, MD; Mitsunobu Enomoto, MD; Hiroshi Aoyama, MD; Satoshi Yamaji, MD; Katsuaki Yokoyama, MD; Hiroshi Yagi, MD; Toshio Kushiro, MD; Atsushi Hirayama, MD

**Background** It has been reported that bepridil is as good as amiodarone in converting persistent atrial fibrillation (AF) to sinus rhythm (SR). The conversion effect of bepridil alone is not always satisfactory, however. The efficacy of pharmacological cardioversion by the combination of bepridil and a class Ic antiarrhythmic drug for persistent AF is studied.

**Methods and Results** The participants comprised 37 consecutive patients in whom pharmacological cardioversion was conducted to treat persistent AF (duration 22.5 ± 29.6 months). Each patient first received a class Ia or Ic antiarrhythmic drug, then bepridil alone, then a combined therapy of bepridil at 200 mg/day with a class Ic antiarrhythmic drug at a routine dose. Unaccompanied use of any of the antiarrhythmic drugs achieved pharmacological cardioversion in 14 (38%) of the 37 patients (single therapy group), whereas SR was restored by combination of bepridil and a class Ic antiarrhythmic drug in 22 (combined therapy group) of the remaining 23 patients. The duration of AF was significantly longer in the combined therapy group than in the single therapy group (28.3 ± 31.0 vs 7.3 ± 4.1 months).

**Conclusion** Combined therapy of bepridil and a class Ic antiarrhythmic drug is efficient for pharmacological cardioversion of refractory long-lasting persistent AF. (Circ J 2008; 72: 709–715)

**Key Words:** Bepridil; Class Ic antiarrhythmic drug; Persistent atrial fibrillation; Pharmacological cardioversion

The longer the duration of persistent atrial fibrillation (AF), the less likely that a class I antiarrhythmic drug will induce pharmacological cardioversion. However, some reports have shown that oral administration of class III antiarrhythmic drugs, including dofetilide and amiodarone, can restore sinus rhythm (SR) in 30–63% of patients with long-lasting persistent AF. Other reports have recently shown that bepridil, which is a multi-channel blocker acting to block calcium, potassium and sodium channels, and has characteristics similar to those of class III antiarrhythmic drugs, also effects pharmacological cardioversion in a manner similar to that of class III antiarrhythmic drugs. Bepridil’s success rate is, at most, 34–58%; hence, the conversion effect of bepridil alone is not always satisfactory.

It is predicted that blocking of the sodium channel, which is effected by bepridil only weakly, is better accomplished by the combined use of bepridil with a class Ic antiarrhythmic drug, improving the conversion effect. We suggest that the combined therapy of bepridil and a class Ic antiarrhythmic drug should safely improve the rate of pharmacological cardioversion in patients with normal cardiac function, whereas class Ic antiarrhythmic drugs may exacerbate cardiac dysfunction in patients with cardiac functional disturbances.

The present study investigates the efficacy of pharmacological cardioversion by the combination of bepridil and a class Ic antiarrhythmic drug for persistent AF in patients with normal cardiac function, in whom single antiarrhythmic drug therapy with class I antiarrhythmic drugs or bepridil failed to restore SR.

**Methods**

The participants comprised 37 consecutive patients with persistent AF (33 men and 4 women; mean age 60.2 ± 10.0 years; range 39–79 years) who had symptoms of AF, and were referred to our hospital for pharmacological cardioversion. In the present study, all patients had had persistent AF for at least 3 months. The duration of AF was confirmed by ECG recordings; the mean duration was 22.5 ± 29.6 months (range 3–107 months). Before treatment, all patients underwent a 12-lead body surface ECG, trans-thoracic and transesophageal echocardiography, and biochemical and hematological examination. Exclusion criteria were: (1) age >80 years; (2) confirmation of a thrombus in the left atrium by transesophageal echocardiography; (3) left ventricular ejection fraction (LVEF) <50%; (4) QT interval >0.45 s on baseline ECG; (5) a history of serious cardiovascular events within the previous 3 months; and (6) a history of sinoatrial node dysfunction. Anticoagulation therapy (warfarin) was administered to all patients, and the
international normalized ratio (INR) was controlled at approximately 2.0 during treatment. Participants were allowed to continue receiving the following drugs: AT-II receptor antagonists and angiotensin-converting enzyme inhibitors to control blood pressure; Ca antagonists and \( \beta \)-blockers to control heart rate; and statins to treat hyperlipidemia.

After informed consent was given, treatment with antiarrhythmic drugs was started in each patient, according to the study’s protocol. The protocol for antiarrhythmic drug administration was as follows: A class Ia or Ic antiarrhythmic drug alone was administered first at a routine dose (Ia, cibenzoline 300 mg/day; Ic, pilsicainide 150 mg/day or flecainide 200 mg/day). If SR was not restored after 4 weeks of administering a class Ia or Ic antiarrhythmic drug, those drugs were stopped and therapy with bepridil was commenced. Bepridil was administered at 100 mg/day for the first 2 weeks. After confirming the QT interval to be within 0.50 s, the daily dose was increased to 200 mg. If bepridil failed to restore SR after 8 weeks of administration, a class Ic antiarrhythmic drug (ie, pilsicainide or flecainide) was added to the bepridil (200 mg/day). Pilsicainide was started at 75 mg/day and flecainide was started at 100 mg/day. After 2 weeks pilsicainide was increased to 150 mg/day and flecainide was increased to 200 mg/day.

During treatment with oral antiarrhythmic drugs, all patients began receiving regular medical examinations every 2–4 weeks as outpatients, to assess the efficacy of the treatment and to check for adverse events. The 12-lead body surface ECG was recorded to evaluate the treatment’s efficacy, and heart rate, QRS width, and QT interval were measured. During AF, the QT intervals were measured in 10 beats on the ECG, and then averaged. Biochemical examination included the measurements of plasma atrial natriuretic peptide (ANP) concentration and brain natriuretic peptide (BNP) concentration, to assess cardiac function.

When administration of an antiarrhythmic drug caused persistent AF, 37 patients (Ia or Ic AAD: pilsicainide:16, flecainide:10, cibenzoline:11) were converted to sinus rhythm (SR) with single antiarrhythmic drug (AAD) therapy with class I AADs or bepridil. In 22 (96%) of the remaining 23 patients, AF converted to SR with a combination of bepridil and a class Ic AAD.

![Figure 1. Outcome of pharmacological conversion of persistent atrial fibrillation (AF). In 37 patients, 14 (38%) were converted to sinus rhythm (SR) by single antiarrhythmic drug (AAD) therapy with class I AADs or bepridil. In 22 (96%) of the remaining 23 patients, AF converted to SR with a combination of bepridil and a class Ic AAD.](image-url)
the QT interval to increase to >0.50 s or the QRS width to increase to >0.12 s, either the dose was decreased or administration was immediately discontinued. The targeted level for serum potassium was >4.0 mmol/L.

All variables are expressed as the means ± SD. Statistical analysis was conducted using the non-parametric test and results were considered to be significant at p<0.05.

**Results**

Persistent AF was converted to SR in 5 of the 37 patients by class I antiarrhythmic drugs (cibenzoline, 1 patient;
flecainide, 4 patients), and in 9 patients by bepridil alone. Consequently, single therapy with any of the antiarrhythmic drugs used here achieved pharmacological cardioversion in 14 (38%) of the 37 patients, whereas SR was restored by a combination of bepridil and a class Ic antiarrhythmic drug in 22 (flecainide, 14 patients; pilsicainide, 8 patients) of the remaining 23 patients (Fig 1). In the one patient in whom a combination of bepridil and a class Ic antiarrhythmic drug failed to give SR, SR could not be restored even by a combination of bepridil and aprindine, or by amiodarone alone.

Table 1 shows the backgrounds of the 14 patients in whom SR was restored by single antiarrhythmic drug therapy alone (ie, single drug group), and the 22 patients in whom SR was restored by a combination of bepridil and a class Ic antiarrhythmic drug (ie, combined therapy group). There were no significant differences between the 2 groups for age, gender, underlying disease, ECG findings, or LVEF or left atrial diameter as determined by echocardiographic findings. Plasma ANP concentration was significantly lower in the combined therapy group than in the single drug group. There was no significant difference in plasma BNP concentration between the 2 groups, however. The duration of AF was significantly shorter in the single drug group (7.3±4.1 months, range 3–15 months) than in the combined therapy group (28.3±31 months, range 5–93 months) (see Table 1, Fig 2).

In the combined therapy group, the duration of AF was ≤15 months in 14 patients (mean duration of AF, 8.7±2.9 months; NS vs single drug group). In this subgroup of the combined therapy group, the plasma ANP concentration (61.0±34.1 pg/ml) was significantly lower than that in the single drug group, despite the similar short duration of AF. One of the patients (a 56-year-old man), in whom pharmacological cardioversion was not achieved, had a history of AF lasting 107 months, which is the longest duration in the present study’s entire cohort. This patient did not have left ventricular hypertrophy, and LVEF was 64.4%, left atrial diameter was 45.4mm, and plasma concentrations of ANP and BNP were, respectively, 38 pg/ml and 140.1 pg/ml.

Fig 3 shows ECG changes during the therapeutic period in a typical case from the combined therapy group. Fig 4 shows changes in ECG findings in the single drug group and combined therapy group. The R–R interval, the QRS width and the QT interval were also significantly extended after conversion to sinus rhythm. The QRS width was significantly longer in the combined therapy group than in the single therapy group, whereas there was no significant difference in QT interval between the 2 groups. *p<0.05 vs control. AAD, antiarrhythmic drug.
10.2 ms in class I antiarrhythmic drug; 89±10.5 to 95.3±6.6 ms in bepridil; and 99.3±16.3 to 118.4±26.6 ms in the combined therapy group; QT interval: 354.6±14.2 to 425.8±17.8 ms in class I antiarrhythmic drug; and 354.0±30.9 to 445.3±23.3 ms in bepridil; and 355.8±24.1 to 418.0±36.4 ms in the combined therapy group). The QTc was not significantly different between at baseline and during the therapeutic period (class I antiarrhythmic drug 0.420±0.016 to 0.430±0.019; bepridil 0.415±0.048 to 0.412±0.020; combined therapy 0.417±0.034 to 0.426±0.041). The QRS width was significantly longer in the combined therapy group than in the single therapy groups, whereas there was no significant difference in R–R interval, QT interval and QTc among the groups.

The plasma ANP and BNP concentrations were significantly reduced immediately after restoration of SR in both groups (ANP: 96.2±25.3 to 36.3±16.1 pg/ml in the single drug group and 53.3±29.1 to 21.2±9.1 pg/ml in the combined therapy group; BNP: 127.7±68.9 to 40.7±17.9 pg/ml in the single drug group and 139.0±118.3 to 38.8±31 pg/ml in the combined therapy group) (Fig 5).

During treatment with the antiarrhythmic drugs, serum potassium was controlled at 4.3±0.2 mmol/L. There were no pro-arrhythmic adverse effects, such as torsades de pointes or transient cardiac arrest. Asymptomatic sinus bradycardia (total heart rate <80,000 beats; daytime heart rate at rest <50 beats/min) was observed immediately after restoration of SR in only one patient who received combined therapy with bepridil and flecaïnide.

During a mean follow-up period of 14.6±8.5 months after pharmacological cardioversion, SR was maintained in 3 of the 5 patients on continuous class I antiarrhythmic drugs, in 8 of the 9 patients on continuous bepridil, and in 21 of the 22 patients on continuous combined therapy with bepridil and a class Ic antiarrhythmic drug.

**Discussion**

In the present study, pharmacological cardioversion was achieved by single antiarrhythmic drug therapy with class I antiarrhythmic drugs or bepridil in 14 (38%) of 37 patients with persistent (>3 months) AF without cardiac dysfunction (LVEF >50%). In contrast, AF converted to SR with a combination of bepridil and a class Ic antiarrhythmic drug in 22 (96%) of the 23 patients who did not respond to single antiarrhythmic drug therapy.

AF is associated with shortening of the duration of the action potential in the process of electrical remodeling. In the long term, L-type calcium channel downregulation and in the short term a transient increase of Kv 1.5-channel current, play an important role in electrical remodeling. Bepridil has multiple ion-channel blocking effects that include potassium, calcium and sodium channels. Although the detailed mechanism of the effect of bepridil for persistent AF has not been clarified, 2 mechanisms are proposed. In the first, the blocking action of bepridil on potassium currents, including Ik,A, Ik,C, Ik,S, Ik,K, IKATP and IKAch, prolongs the action potential duration of the atrium. The second mechanism by which bepridil might terminate AF is that the blocking action of bepridil on the type T and L-type calcium channel, as well as its blocking action on the Kv 1.5-channel current, reverse the electrical remodeling.

Nakazato et al reported that, in 65 of 112 (58%) patients with persistent AF lasting an average of 5.2 months, SR was restored by oral administration of bepridil. Fujiki et al found that in patients with persistent AF lasting an average of 49 months, SR was restored by bepridil alone (34%) or in combination with aprindine class Ib antiarrhythmic drug (35%). In the present study, bepridil alone restored SR in 9 of 32 patients (28%) who had not experienced SR restoration by Ia or Ic drug therapy alone. These results indicate that the effect on persistent AF of extended duration of pharmacological cardioversion by bepridil alone is limited. This limitation may be due to the weak sodium channel-inhibiting effect of bepridil. A class Ic antiarrhythmic drug will compensate for the inadequate effect of bepridil on the sodium channel, and can restore SR even in those patients with long-lasting persistent AF with no marked prolongation of the QT interval, when used in combination with bepridil.

The rate of pharmacological cardioversion when combining bepridil with a class Ic antiarrhythmic drug was 96% – a highly favorable result. The duration of AF in the
present study’s cohort differed from that reported by Fujiki et al.4,12 Our therapeutic strategy, using a combined therapy of bepridil and a class Ic antiarrhythmic drug for pharmacological cardioversion of AF, appears to be superior to combined therapy with bepridil and aprindine, as used by Fujiki and colleagues5,12. The present study’s results suggest that potent blocking action of the sodium channel, as well as the blocking of potassium currents, is necessary for pharmacological cardioversion of persistent AF, regardless of the duration of AF. The inhibitory action of flecaïnide on multiple channels, including both the sodium channel and the potassium channel, may be involved in the combined action of bepridil with flecaïnide.

Two differences in background characteristics were observed between the single drug group and the combined therapy group. Patients in the combined therapy group had a longer period of persistent AF and a lower plasma ANP concentration than those in the single drug group. Single antiarrhythmic drug therapy may have a limited effect on the restoration of AF in patients with long-lasting AF or with a low plasma ANP concentration.

Plasma ANP is produced in response to stretching of the atrium. Acute AF leads to an increase in plasma ANP concentration13 but prolonged AF is associated with a reduced capacity of the atria to produce ANP. Therefore, an inverse relationship exists between the duration of AF and plasma ANP concentration.14 It has also been reported that, in patients with failed electrical cardioversion or recurrent AF, the plasma ANP concentration did not increase during exercise prior to cardioversion, whereas a normal increase was observed in patients with successful cardioversion.15 Furthermore, pre-operative plasma ANP concentration is high and the duration of AF is short in patients in whom SR can be maintained by Maze’s operation, compared to patients with recurrent AF.16

In the present study, there was a subgroup in which single antiarrhythmic drug therapy failed to restore SR, although the duration of AF was relatively short. A total of 14 patients, with an AF duration of ≤15 months, similar to the single drug group, and in whom combined therapy was needed for restoration of SR, had lower plasma ANP levels than those in the single drug group. Since degeneration of the atrial muscle progresses rapidly even when the duration of AF is short, there may be some patients in whom single antiarrhythmic drug therapy does not achieve restoration of SR. On the basis of these observations, the plasma ANP concentration provides treatment guidelines for pharmacological cardioversion.

Plasma ANP and BNP concentrations decrease immediately when AF is converted to SR in response to electrical cardioversion7,18. In the present study, plasma ANP and BNP concentrations decreased rapidly after restoration of SR, indicating that cardiac function is improved markedly by restoration of SR with pharmacological cardioversion using antiarrhythmic drugs. Serious adverse effects of bepridil have been reported, however. In particular, sinus kalemia, particularly in elderly female patients. In the present study, subjects over 80 years of age were excluded, and efforts were made to avoid serum potassium decreases. Furthermore, the daily dose of bepridil was, at most, 200 mg, and the dose was immediately reduced in those patients who showed an increase in the QT interval. These reasons may explain the absence of any serious adverse effects, such as torsades de pointes, in the present study’s cohort.

The present study found that combined therapy using bepridil and a class Ic antiarrhythmic drug is efficient in causing pharmacological cardioversion in patients with refractory persistent AF that is unresponsive to single antiarrhythmic drug therapy with class I antiarrhythmic drugs or bepridil alone. The effect of combined therapy on sustaining SR after cardioversion remains unknown. Cardiac function showed improvement immediately after restoration of SR, but the effect on cardiac function by long-term combined therapy with antiarrhythmic drugs remains unclear. It is necessary to investigate and resolve these issues by observing the post-cardioversion course.

Conclusion

Combined therapy with bepridil and a class Ic antiarrhythmic drug has been shown to be excellent in generating cardioversion of refractory long-lasting persistent AF, which is unresponsive to single antiarrhythmic drug therapy with class I antiarrhythmic drugs or bepridil. This combination provides an efficient therapeutic method for improving cardiac function by restoration of SR in AF patients without pro-arrhythmic adverse effects.

References


*Pharmacological Cardioversion of Persistent AF*