Beta-Blocker Decreases the Increase in QT Dispersion and Transmural Dispersion of Repolarization Induced by Bepridil

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Bepridil is effective for intractable cardiac arrhythmia, but in rare cases will induce torsades de pointes (TdP) associated with QT interval prolongation. Beta-blockers will effectively prevent TdP in some clinical settings, so the effect of β-blocker on the change in QT interval, QT dispersion and transmural dispersion of repolarization (TDR) induced by bepridil was investigated in 10 patients (7 male, 3 female; 62±6 years old) with intractable paroxysmal atrial fibrillation. The QTc interval, QTc dispersion and TDR were measured before and after 1 month of administration of bepridil, and then a β-blocker was added and the QTc interval, QTc dispersion and TDR re-measured 1 month later. Bepridil significantly prolonged the QTc interval (0.42±0.05 to 0.50±0.08; p<0.01), and increased both the QT dispersion (0.07±0.05 to 0.14±0.08; p<0.01) and TDR (0.10±0.04 to 0.16±0.05; p<0.01). The addition of a β-blocker decreased the QTc interval (0.50±0.08 to 0.47±0.04; p=0.09) and significantly decreased both the QTc dispersion (0.14±0.08 to 0.06±0.02; p<0.01) and TDR (0.16±0.05 to 0.11±0.04; p<0.001). Compared with the control, the combination therapy significantly prolonged the QTc interval, but did not increase either QTc dispersion or TDR, and so was effective in all patients with intractable AF. The findings suggest that β-blocker reduces the increase in QT dispersion and TDR induced by bepridil, and combined therapy with bepridil and β-blocker might thus be useful for intractable atrial fibrillation. (Circ J 2002; 66: 1024–1028)

Key Words: β-blocker; QT interval; QT dispersion; Repolarization; Transmural dispersion

Amiodarone is effective for intractable cardiac arrhythmia, decreasing the mortality1–4 and it is also effective in the prevention of paroxysmal atrial fibrillation (AF) resistant to class Ia antiarrhythmic drugs5,6. However, it has severe extra-cardiac adverse effects, such as pulmonary fibrosis and hyperthyroidism, and there is a need for drugs that are effective for intractable paroxysmal AF without side effects. Bepridil is effective for intractable cardiac arrhythmia and does not severe extra-cardiac adverse effects, but can induce torsades de pointes (TdP) associated with QT interval prolongation7–9. In general, TdP is associated with QT prolongation and/or increase in QT dispersion10 and/or transmural dispersion of repolarization (TDR)11–13. QT dispersion is a fairly good marker of patients at high risk for serious ventricular arrhythmia and sudden death14. On the other hand, β-blockers can prevent the occurrence of TdP associated with QT interval prolongation11 and TdP is less common with amiodarone than with other class III agents15 because of its β-blocking effects and reduction of QT dispersion and TDR in the human heart16–18; Therefore, it is possible that the combination of a β-blocker and bepridil would be effective for intractable cardiac arrhythmia without severe extra-cardiac adverse effects or induction of TdP. However, there is little information available on the effect of bepridil on QT dispersion and TDR or the effects of adding a β-blocker to the therapy, and we therefore investigated this.

Methods

Patients

The subjects were 10 patients (7 male, 3 female; 62±6 years old) with intractable paroxysmal AF resistant to more than 3 types of Vaughan-Williams classification Ia, Ic and II drugs. Three patients had valvular disease, 2 had hypertrophic cardiomyopathy, 1 had ischemic heart disease and the other 4 did not have cardiac disease.

Bepridil was given at 100–200mg/day for 1 month and the QTc interval, QTc dispersion and TDR were measured before and after the 1-month of administration. We then added a β-blocker to the bepridil therapy for a further month and re-measured the QTc interval, QTc dispersion and TDR. The β-blockers given were either metoprolol at 30–40mg/day (6 patients) or bisoprolol at 2.5–5mg/day (4 patients) (Table 1).

We interviewed patients about palpitations or chest discomfort associated with AF before and 1 month after the administration of the drugs and we defined the effectiveness of the drug for paroxysmal AF as a decrease in the frequency of symptoms related to paroxysmal AF to less than 40% of that in controls after drug administration.

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None of the patients had abnormal concentrations of electrolytes, symptoms of heart failure or ischemia during this study.

**ECG Interval Measurements**

Standard 12-lead ECGs were performed at a paper speed of 25 mm/s within 1 month of administration of bepridil as well as 1 month after the addition of the \( \beta \)-blocker. The ECG interval measurements were performed by an observer unaware of the therapies. The RR intervals, TpTe intervals (from the peak of T wave to the end of T wave) were measured during sinus rhythm in lead II; the QT interval was measured during sinus rhythm in all leads; the T wave end (= Te) was defined as the point at which the terminal T wave returned to the baseline. When a U wave was present and interrupted the T wave, the terminal portion of the visible T wave was extrapolated to the baseline to identify the T wave end. The difference between maximum and minimum precordial QT intervals on each ECG was defined as regional QT dispersion. The QT interval, QT interval dispersion, and TDR were corrected for the patient’s heart rate using Bazett’s formula: 

\[
QTc = \frac{QT}{\sqrt{RR}}
\]

**Statistics**

Statistical analysis of data was performed using Student’s t-test for paired data. Values are expressed as mean±SD. Finding p<0.05 was considered significant.

**Results**

**Clinical Results**

Bepridil was effective for intractable paroxysmal AF in 8 cases, and the addition of \( \beta \)-blocker (metoprolol) decreased the frequency of episodes of palpitations in the remaining 2 (case no’s. 8, 10) (Table 1).

**ECG Measurements After Drug Administration**

Bepridil significantly prolonged the QTc interval (0.42±0.05 to 0.50±0.08; p<0.01) and increased both QTc dispersion (0.07±0.05 to 0.14±0.08; p<0.01) and TDR (0.10±0.04 to 0.16±0.05; p<0.01). The addition of \( \beta \)-blocker significantly decreased the QTc dispersion (0.14±0.08 to 0.06±0.02; p<0.01) and TDR (0.16±0.05 to 0.11±0.04; p<0.001), and also decreased the QTc interval (0.50±0.08 to 0.47±0.04; p=0.09), but not to a significant extent. Compared with the controls, the combination therapy significantly prolonged the QTc interval (p<0.01), but increased neither QTc dispersion nor TDR (Fig 1).

Bepridil significantly increased the maximum of QTc (0.47±0.07 to 0.56±0.09; p<0.05), but there was no significant change in the minimum of QTc (0.40±0.04 to 0.42±0.03; p=0.21). Addition of a \( \beta \)-blocker significantly decreased the maximum of QTc (0.56±0.09 to 0.51±0.06; p<0.05), but there was no significant change in the minimum of QTc (0.42±0.03 to 0.45±0.05; p=0.09).

Neither bepridil nor the combination therapy changed the RR interval (1.00±0.26 to 0.92±0.10; p=0.38, to 1.06±0.16; p=0.50) or the QRS interval (0.09±0.02 to 0.09±0.02;
Effects of Bepridil and Torsades de Pointes on Electrophysiological Properties

In many clinical settings, TdP occurs in association with QT prolongation, such as in the congenital disease Romano-Ward syndrome and with the hypokalemia or bradycardia induced by antiarrhythmic drugs. The electrophysiological mechanism of TdP at the cellular level is still uncertain. Several investigators recently reported that TdP is induced by early afterdepolarization in M cells.11-13 Furthermore, this early afterdepolarization originates in the gradient between M cells and epicardial cells and is accelerated by an increase in TDR. Therefore, an increase in QT dispersion and TDR are important predictive markers of the induction of TdP by antiarrhythmic drugs.14,19

Beta-blockers prevent TdP in long QT syndrome, but does not inhibit IKr.20 The IKr density in epicardial, endocardial and M cells is similar, whereas the IKs density is significantly lower in M cells. Specific IKs blockers prolong the QT interval and the action potential duration in these 3 types of cells, and therefore do not increase transmural dispersion.21 On the other hand, specific IKr blocking agents caused preferential prolongation of the M cell action potential duration, giving rise to broad and sometimes low-amplitude bifurcated T waves and increased transmural dispersion.22 Therefore, drugs such as bepridil that have only the IKs blocking effect at a clinical therapeutic concentration probably do not change the TDR. However, our data suggested that bepridil increased TDR. The other blocking effect of current, such as INa, ICa, and IK1, may be associated with the increase of TDR, low amplitude T wave and bifurcated T wave. Precordial QT interval dispersion corresponds to regional variabilities in the repolarization time of M cells.14,19 Though the mechanism of the increase of QT dispersion by bepridil is still unknown, but may be related to an increased spatial heterogeneity of repolarization that can be a substrate for TdP.22

Discussion

Bepridil and Torsades de Pointes

Significant clinical utility of the calcium antagonist bepridil has been demonstrated for chronic stable angina; during controlled and long-term extended angina trials in 840 patients, 24 cases of ventricular tachycardia, 2 of paroxysmal atrial fibrillation, and 7 of TdP were reported and of these potentially serious ventricular arrhythmias, 20 were considered probably or possibly related to therapy.9 The incidence of serious ventricular arrhythmias was approximately 2.4%, with TdP occurring in 7 patients who received a daily dose of bepridil of 200 mg or more (200 mg in 2,300 mg in 2,400 mg in 2,600 mg in 1) and who had a QT/QTc greater than 0.57. Bepridil induced TdP at these doses, so it is possible that a low dose is safe and effective in properly selected patients despite the increase in QT dispersion and TDR it induces.

Effects of Bepridil and Torsades de Pointes on Electrocardiogram

Several investigators recently reported that TdP is induced by early afterdepolarization in M cells.11-13 Furthermore, this early afterdepolarization originates in the gradient between M cells and epicardial cells and is accelerated by an increase in TDR. Therefore, an increase in QT dispersion and TDR are important predictive markers of the induction of TdP by antiarrhythmic drugs.14,19

Bepridil at a clinical therapeutic concentration blocks IKs, but does not inhibit IKr.20 The IKr density in epicardial, endocardial and M cells is similar, whereas the IKs density is significantly lower in M cells. Specific IKs blockers prolong the QT interval and the action potential duration in these 3 types of cells, and therefore do not increase transmural dispersion.21 On the other hand, specific IKr blocking agents caused preferential prolongation of the M cell action potential duration, giving rise to broad and sometimes low-amplitude bifurcated T waves and increased transmural dispersion.22 Therefore, drugs such as bepridil that have only the IKs blocking effect at a clinical therapeutic concentration probably do not change the TDR. However, our data suggested that bepridil increased TDR. The other blocking effect of current, such as INa, ICa, and IK1, may be associated with the increase of TDR, low amplitude T wave and bifurcated T wave. Precordial QT interval dispersion corresponds to regional variabilities in the repolarization time of M cells.14,19 Though the mechanism of the increase of QT dispersion by bepridil is still unknown, but may be related to an increased spatial heterogeneity of repolarization that can be a substrate for TdP.22

Effects of ß-Blocker on Changes in QT Interval, QT Dispersion and Transmural Dispersion

Beta-blockers prevent TdP in long QT syndrome, but the mechanism is still unclear. One possibility is decreasing the QT interval and QT dispersion. However, some investigators have proposed that ß-blockers can effectively prevent TdP without decreasing the QT interval and QT dispersion.19 In the present study, the addition of a ß-blocker to bepridil therapy significantly decreased QTc dispersion. Bepridil significantly increased the maximum of QTc, but there was no significant change in the minimum. The addi-
tion of a ß-blocker significantly decreased the maximum of QTc, but there was no significant change in the minimum. Therefore, QTc dispersion increased after administration of bepridil, and decreased after the addition of a ß-blocker. Thus, the change in QTc dispersion mainly reflects the change in the maximum of QTc, suggesting that the effect of bepridil and ß-blocker on regional M cells is the most important factor in the change of QTc dispersion.

The functional link between IKr and the ß-adrenergic receptor may play an important role in arrhythmogenesis and contribute to the antiarrhythmic action of clinically used ß-blockers.23 Sympathovagal imbalance may also have an important role in the dynamic change in QT interval and initiation of TdP in patients with long QT syndrome.24

In an experimental study, administration of isoproterenol in the continued presence of IKs blocking agents decreased the action potential duration of epicardial and endocardial cells, but not that of M cells, resulting in widening of the T wave and dramatic accentuation of transmural dispersion.11 On the other hand, ß-blockers can decrease transmural dispersion. In fact, it has been reported that amiodarone, which has ß-blocker effects, reduced QT dispersion and the transmural heterogeneity of repolarization, despite prolongation of the QTc interval.16 In our current study, the addition of ß-blocker to bepridil also significantly decreased QT dispersion and TDR. Furthermore, it has been reported that ß-blockers reduce QT dispersion in patients with chronic heart failure25 and hypertrophic cardiomyopathy.26

Combination Therapy With Bepridil and ß-Blocker

Amiodarone has blocking effects not only of IKr, IKs, and Ito, but also of the ß- and ß-adrenergic receptors, and bepridil blocks IKr, IKs, Ito and IK1.27 Thus, the greatest difference in the channel-blocking effects between amiodarone and bepridil appears to be the ß-blocking effects.

Because the ß-blockers decrease the increase of QT dispersion and TDR induced by bepridil, combined therapy with bepridil and ß-blockers may reduce the risk of proarrhythmic events such as TdP as effectively as amiodarone.15

Study Limitations

First, the QT interval measurements were performed manually. When T wave are low in amplitude and bifurcated, as after bepridil administration, the manual measurement of the QT interval and TDR may not be reliable because of difficulties in exactly determining the T wave. Second, the patients receiving combination therapy had different dose rates and type of ß-blockers. Third, we did not measure drug concentrations.

In summary, bepridil alone and the combination therapy prolonged the QTc interval. Bepridil significantly increased QTc dispersion and the TDR, but the combination therapy did not significantly change them. The addition of a ß-blocker to bepridil decreased the magnitude of the increase in QT dispersion and TDR that were induced by bepridil. Thus, the combined therapy may be useful for preventing arrhythmias without induction of TdP.

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1028


