Opposing Effects of Bepridil on Ventricular Repolarization in Humans

—— Inhomogeneous Prolongation of the Action Potential Duration vs Flattening of Its Restitution Kinetics ——

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Background: Bepridil is highly effective in the treatment of atrial fibrillation, but its clinical usefulness is limited by a potential risk for the drug-induced torsades de pointes (TdP) in association with its Class III action.

Methods and Results: Monophasic action potentials (MAPs) were recorded from the right ventricular outflow tract (RVOT) and apex (RVA) in 9 patients treated with bepridil (172±26 mg/day) and 10 control patients. Bepridil significantly increased the steady-state MAP durations at 90% repolarization (MAPD90) in a rate-independent manner at pacing cycle lengths ranging from 330 to 750 ms. The bepridil-induced prolongation of the MAPD90 was greater in RVOT (~13%) than RVA (~8%). Bepridil flattened the MAPD90 restitution slope estimated by an S1–S2 protocol in both the RVOT (0.65±0.22 vs 0.95±0.38) and RVA (0.65±0.14 vs 0.94±0.29). The Tpeak-end interval in the ECG was increased by bepridil for S1 but not S2 at the shortest diastolic interval to produce a ventricular response.

Conclusions: Bepridil produces an inhomogeneous prolongation of the MAPDs, but flattens their restitution kinetics in the human ventricle. The former effect would favor the functional reentry predisposing to TdP, whereas the latter one would counteract that by reducing the dynamic instability of the repolarization. (Circ J 2009; 73: 1612–1618)

Key Words: Bepridil; Monophasic action potential; QT prolongation; Repolarization; Torsades de pointes

Recent clinical studies have shown that bepridil, a multichannel blocker, is highly effective for the conversion of long-lasting persistent atrial fibrillation (AF) and the maintenance of sinus rhythm.1–9 Despite its usefulness for the treatment of AF, there remains some concern about the drug-induced polymorphic ventricular tachycardia, known as torsades de pointes (TdP), in association with QT prolongation.10–13 The QT prolongation is attributable to the blockade of several K+ outward currents, including the rapidly and slowly activating delayed rectifier K+ currents (IKr and IKs).2–5 Spatially inhomogeneous prolongation of ventricular action potential duration (APD) through an inhibition of IKr (with or without concomitant inhibition of IKs) can provide a substrate for functional reentry leading to TdP.14–16 A number of theoretical and experimental studies have revealed that dynamic instability of repolarization represented by electrical restitution is also important for determining the propensity for functional reentry.17–24 As to the effects of bepridil on the spatial inhomogeneity and dynamic instability of repolarization in the human ventricle, however, the available information is still limited and much remains to be clarified.

To address this issue, we investigated the effects of bepridil on the monophasic action potentials (MAPs) in the human ventricle in terms of their regional differences and dynamic properties.

Methods

Nine patients treated with bepridil (172±26 mg/day for 6±3 months) for paroxysmal AF and 10 control patients without bepridil were enrolled. Of the 10 control patients, 5 had atrioventricular nodal reentrant tachycardia and 5 had atrioventricular reciprocal tachycardia. All of the patients were admitted to Shizuoka Saiseikai General Hospital (Shizuoka, Japan) for an electrophysiological study and/or catheter ablation. They were male and their mean age was 58±10 and 60±10 years for the control and bepridil group, respectively (P=0.47). None had structural heart disease. The left ventricular ejection fractions were 70±5 and 69±3% for the control and bepridil group, respectively (P=0.46). The study protocol was approved by the Institutional Ethics Committee of the hospital, and all patients gave their written informed consent.
MAP Recordings
MAP recordings were performed under mild sedation (midazolam 0.5–1.5 mg/h IV). In the 10 control patients, MAPs were recorded during the waiting period after the ablation procedure targeting the respective tachyarrhythmia. Of the 9 patients treated with bepridil, MAP recordings were carried out as a part of the electrophysiological study for syncope of unknown origin in 3, and during the waiting period after pulmonary vein isolation in 6. All antiarrhythmic drugs except bepridil were withheld for periods of at least 5 times their half lives before the procedure. A steerable Franz catheter was inserted via the femoral vein into the right ventricle (RV) and MAPs were recorded sequentially from the outflow tract (RVOT) and the apex (RVA) via a pair of Ag-AgCl electrodes mounted near the tip of the catheter. The MAP recording site was paced via a pair of electrodes on the same catheter at 5 different cycle lengths (CLs) of 750, 600, 500, 400, and 330 ms for 30 s to reach a steady state at the respective CL. The pulses used for pacing were 1 ms in duration and twice the diastolic threshold in intensity. The MAP durations at 50% and 90% repolarization (MAPD50 and MAPD90, respectively) were measured manually in the last 10 consecutive beats at the respective pacing CL and then averaged.

When the effective refractory period (ERP) was measured at the MAP recording site, eight basic stimuli (S1) at a CL of 600 ms were followed by a premature stimulus (S2) with progressive shortening of the S1–S2 coupling interval in 20-ms steps from 500 to 400 ms, in 10-ms steps from 400 ms to 350 ms, and in 5-ms steps from 350 ms to the refractory point. The ERP was defined as the longest S1–S2 interval that failed to produce a ventricular response (the ERP was determined with 5 ms precision). A MAPD90 restitution curve was constructed by plotting S2/MAPD90 against the diastolic interval (DI; the interval from the 90% repolarization of the preceding S1-MAP to the upstroke of the S2-MAP). When S2 was applied before the 90% repolarization of the S1-MAP, the repolarization slope of the S1-MAP was extrapolated to estimate the 90% repolarization point. To obtain the maximum slope (Slope_{max}) of the MAPD90 restitution curve, the data were fitted using overlapping least-squares linear segments; a linear fit was performed in 30-ms DI segments in steps of 10 ms, commencing from the shortest DI range to produce a ventricular response.25,26

The MAP signals filtered between 0.1 and 100 Hz were recorded and stored digitally on an EP lab system (Bard, Billerica, MA, USA). Any MAP traces exhibiting a marked baseline drift, motion artifact or amplitude of <10 mV were excluded from the analysis.

ECG Parameters
ECG data were collected during S1 and S2 at the shortest DI to produce a ventricular response (Di_min) applied to the RVA. The QRS duration, QT interval and JT interval were measured from the standard 6 precordial leads (V1–6). The QT interval was defined as the time interval from the initial deflection of the QRS to the end of the T wave, where a tangent of the terminal slope crosses the isoelectric line. The JT interval was measured as the time interval from the J point to the end of the T wave. We also measured the interval from the peak to the end of the T wave (Tpeak-end). In the case of a negative T wave, the interval from the nadir to the end of the T wave was measured. The leads exhibiting a biphasic or flattened T wave were excluded from the measurement. The Tpeak-end interval was expressed as an averaged value for the measured leads.

Statistical Analysis
The results are presented as the mean±SD unless otherwise stated. Statistical significance was analyzed with a Student’s two-tailed unpaired or paired t-test as appropriate. Analysis of variance followed by Bonferroni’s test was used for multiple comparisons. The difference was considered significant at a P<0.05.

Results

Effect of Bepridil on the Steady-State MAP
All patients had regular sinus rhythm at the time of the electrophysiological study. The sinus CLs were 826±42 ms and 88±80 ms, and blood pressures (BPs) were 131±7/80±8 mmHg and 133±10/78±7 mmHg for the control and bepridil-treated patients, respectively, prior to the MAP recordings. The sinus CL in the bepridil-treated patients was significantly longer than that in the control patients

Figure 1. Monophasic action potentials (MAPs) recorded from the right ventricular outflow tract (RVOT) and apex (RVA) in a control patient and a patient treated with bepridil. (A) Representative records from the RVOT (Top) and RVA (Bottom) at pacing cycle lengths (CLs) of 330 ms (Left) and 750 ms (Right). The traces in the 2 patients are superimposed for comparison. (B) MAP durations at 50% and 90% repolarization (MAPD50 and MAPD90, respectively) at 5 pacing cycle lengths (CLs 330–750 ms) in the 2 patients (open symbols: control, closed symbols: with bepridil). Con, control; Bep, bepridil.
The sinus CLs and BP in the respective patients remained unchanged until the end of the MAP recordings (828±64 ms and 133±12/78±6 mmHg for the control group, 883±66 ms and 131±14/78±6 mmHg for the bepridil group, respectively).

Figure 1A shows representative MAP traces recorded from the RVOT and RVA in a control and a bepridil-treated patient. The steady-state values for the MAPD at CLs ≥500 ms in the RVOT, whereas no significant difference was recognized between the 2 groups at any CL tested in the RVA.

Table 1 summarizes the steady-state MAPD data obtained from the 10 control and 9 bepridil-treated patients. The MAPD90 values in the bepridil-treated patients were significantly longer than those in the control patients at CLs ≥500 ms in the RVOT, whereas no significant difference was recognized between the 2 groups at any CL tested in the RVA. In the control patients, the MAPD90s in the RVOT and RVA were comparable. In the bepridil-treated patients, the MAPD90s in the RVOT tended to be longer than those in the RVA, but the difference did not reach a statistical
significance. The MAPD90 values in the bepridil-treated patients were significantly longer than those in the control patients through the entire range of CLs tested both for the RVOT and RVA. In the control group, the MAPD90 in the RVOT and RVA were comparable. In the bepridil-treated group, in contrast, the MAPD90 in the RVOT were significantly longer than those in the RVA except for the longest CL (750 ms, P=0.122). Figure 2 shows the difference in the MAPD90 between the 2 regions (ΔMAPD90). In the control group, the mean ΔMAPD90 was <5 ms (~2–4 ms) at each CL tested, indicating no substantial gradient. In the bepridil-treated group, the mean ΔMAPD90 was much larger (14–18 ms) compared with the control; the difference was statistically significant except for CLs of 500 ms (P=0.079) and 750 ms (P=0.080).

**Effect of Bepridil on the MAPD Restitution**

Figure 3 shows representative MAPD90 restitution curves. The data were obtained from the same patients as presented in Figure 1. In the control patient, the shortest DI to produce a ventricular response (Dmin), and MAPD90 at Dmin (MAPDmin) were ~5 ms and 198 ms, respectively, at the RVOT; the corresponding values at the RVA were ~5 ms and 186 ms. The maximum slope of the MAPD90 restitution curve (Slopenmax) was 1.11 at both the RVOT and RVA. In the bepridil-treated patient, the Dmin in the 2 regions (~10 ms for the RVOT and ~3 ms for the RVA) were similar to the control patient. However, the MAPDmin at the RVOT (248 ms) and RVA (232 ms) were much longer than in the control patient, giving rise to an upward shift in the restitution curves. The Slopenmax in the bepridil-treated patient (0.52 for the RVOT and 0.57 for the RVA) was more flattened than in the control patient.

Table 2 summarizes the restitution parameters obtained from the 10 control and 9 bepridil-treated patients. The ERP and MAPDmin in the bepridil-treated patients were significantly longer, and the Slopenmax in the bepridil-treated patients was significantly less steep than in the control patients for both the RVOT and RVA. The Dmin in the control and bepridil-treated groups were comparable for both the RVOT and RVA. When the 2 regions were compared in the control group, none of the restitution parameters exhibited significant differences. In the bepridil-treated group, in contrast, the MAPDmin and ERP in the RVOT were significantly longer than those in the RVA, whereas no significant regional difference was recognized in the Dmin or Slopenmax.

**Effect of Bepridil on the ECG Parameters**

Table 3 summarizes the ECG parameters during S1 and S2 at the Dmin applied to the RVA. There were no significant differences between the 2 patient groups (with and without bepridil) in the QRS duration during the S1 and S2 stimuli.

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**Table 2.** MAPD90 Restitution Parameters

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<th>RVOT</th>
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<td></td>
<td>ERP (ms)</td>
<td>Dmin (ms)</td>
<td>MAPDmin (ms)</td>
<td>Slopenmax</td>
</tr>
<tr>
<td>Control (n=10)</td>
<td>239±13</td>
<td>-5±4</td>
<td>205±17</td>
<td>0.95±0.38</td>
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<td>Bepridil (n=9)</td>
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<td>4±5</td>
<td>249±17*</td>
<td>0.65±0.22*</td>
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<tr>
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<td>3±7</td>
<td>225±29*#</td>
<td>0.65±0.14*</td>
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Values are mean±SD. *P<0.05 vs control, #P<0.05 vs RVOT. MAPD90, MAPD at 90% repolarization; ERP, effective refractory period; Dmin, shortest diastolic interval to elicit a ventricular response; MAPDmin, MAPD90 at Dmin; Slopenmax, maximum slope of the MAPD90 restitution curve. Other abbreviations see in Table 1.

**Table 3.** ECG Parameters

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<tr>
<th></th>
<th>QRS</th>
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<th>Tpeak-end</th>
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<td></td>
<td>S1</td>
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<td>S2</td>
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<tr>
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<td>168±16*</td>
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<td>504±25*#</td>
<td>315±17</td>
<td>328±22*</td>
<td>162±13*</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P<0.05 vs control, #P<0.05 vs S1. S1, basic stimulus at a cycle length of 600 ms; S2, premature stimulus at the Dmin; Tpeak-end, interval from the peak to the end of the T wave. Other abbreviations see in Tables 1,2.

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Figure 4. S2-induced increases in the interval from the peak to the end of the T wave (Tpeak-end) in the ECG. Percent changes in the Tpeak-end during S2 stimulus at the shortest diastolic interval (Dmin) compared with the corresponding values during S1 stimulus were obtained from the 10 control (open bars) and 9 bepridil-treated patients (solid bars). The values are the mean±SD. *P<0.05 vs control.
Both the QT and JT intervals during the S1 and S2 stimuli in the bepridil-treated patients were significantly longer than those in the control patients. The $T_{\text{peak-end}}$ interval during the S1 stimulus in the bepridil group was significantly longer than that in the control group, whereas the $T_{\text{peak-end}}$ interval during the S2 stimulus did not differ significantly between the 2 groups.

In the both patient groups, the QRS duration and QT interval during the S2 stimulus were significantly longer than those during the S1 stimulus. The JT intervals during the S1 and S2 stimuli did not differ significantly, but there was a trend toward to an increase in the control group ($P=0.067$). The $T_{\text{peak-end}}$ interval during the S2 stimulus was significantly larger than that during the S1 stimulus, but the S2-induced amplification of the $T_{\text{peak-end}}$ interval in the bepridil group (by 61±23%) was significantly less prominent than that in the control group (by 86±23%; $P=0.041$) (Figure 4).

**Discussion**

To the best of our knowledge, this is the first study to reveal the effects of bepridil on the rate-dependent and dynamic properties of the MAPD in the human ventricles. The key observations are as follows. First, bepridil prolonged the steady-state MAPD$_{90S}$ in the RV in a rate-independent manner. Second, the MAPD$_{90}$ prolongation in the RVOT was larger than that in the RVA. Third, bepridil flattened the MAPD$_{90}$ restitution slope. Fourth, in the presence of bepridil, the $T_{\text{peak-end}}$ interval under basic stimulation was longer than the control, but exacerbation of $T_{\text{peak-end}}$ interval in response to premature excitation was less prominent.

**Rate-Independent Prolongation of the MAPD by Bepridil**

Bepridil is an antiarrhythmic drug with a complex pharmacological profile. Bepridil at therapeutic concentrations inhibits the L-type Ca$^{2+}$ current (I$_{\text{Ca,L}}$) and several K$^+$ currents, including I$_{Ks}$, I$_{K}$, the transient outward current (I$_{O}$), the inward rectifier K$^+$ current (I$_{K1}$) and the acetylcholine receptor-operated K$^+$ current (I$_{K,ACb}$) at therapeutic concentrations. Bepridil at higher concentrations inhibits the Na$^+$ current (I$_{Na}$) as well. Bepridil was shown to prolong the APD in the ventricular muscle of guinea pig dog and rabbit. The APD prolongation using bepridil in guinea pig, unlike most of other class III drugs, was not attenuated remarkably at high stimulation rates, suggesting minimal “reverse use-dependence”. Our observation in the human ventricle is concordant with the guinea pig result, because the prolongation of the MAPD$_{90S}$ in the bepridil-treated patients at the shortest and longest CLs tested (330 and 750 ms) was comparable (by 15.0 and 16.8% in the RVOT, and by 8.0 and 10.8% in the RVA compared with the controls). The present study also revealed that the prolongation of the MAPD$_{90}$ by bepridil was appreciably less than that of the MAPD$_{90S}$, possibly reflecting the inhibition of I$_{Ca,L}$. The lack of a reverse use-dependence of the Class III action of bepridil could be attributable to the inhibition of both I$_{K}$ and I$_{Ca,L}$ because the relative contribution of I$_{K}$ on ventricular repolarization is larger at long CLs, whereas that of I$_{Ca,L}$ is larger at short CLs. It is also possible that the inhibition of I$_{Ca,L}$ counteracts an excessive prolongation of the MAPD at longer CLs.

**Inhomogeneous MAPD Prolongation by Bepridil**

In our previous experiments on Langendorff-perfused rabbit hearts, bepridil caused a prolongation of the interval from the peak negative deflection of the QRS complex to the apex of the T wave (Q-aT) in the modified bipolar electrograms recorded from the LV surface, and the Q-aT prolongation, which reflected the APD prolongation, was more prominent in the base than in the apex. In line with this regional difference in the APD prolongation on the apex-base axis, the present study on the human heart has demonstrated that bepridil causes a greater prolongation of the MAPDs in the RVOT than in the RVA. In voltage-clamp experiments on rabbit LV myocytes, Chen et al showed higher I$_{K}$ and lower I$_{Ks}$ densities in the apex than those in the base. Such regional differences in the ionic currents in the ventricle may underlie the spatially inhomogeneous prolongation of the MAPD by bepridil in humans.

In the present study, we did not record the MAPs from the LV. Based on our MAP data obtained from the RV, it seems reasonable to assume that bepridil may increase the spatial heterogeneity of repolarization not only in the RV but also in the LV. To substantiate this assumption, we analyzed the $T_{\text{peak-end}}$ interval. This parameter was proposed originally as an index of transmural dispersion of ventricular repolarization (TDR) based on in vitro experimental studies using LV wedge preparations. However, more recent simulation and experimental studies in in vivo models have suggested that an increase in the $T_{\text{peak-end}}$ interval in body surface ECG does not simply reflect an enhancement of TDR, but represents a more comprehensive spatial heterogeneity of repolarization in the whole ventricles, including the epicardial gradient. The $T_{\text{peak-end}}$ interval in the bepridil-treated group was significantly longer than in the control group during basic (S1) stimulation. This observation is concordant with a previous report by Yoshiga et al, and suggests that bepridil enhances spatial heterogeneity of repolarization not only in the RV but also in the LV.

**Flattening of the MAPD Restitution by Bepridil**

The restitution kinetics of the APD is an important dynamic factor for determining the spatiotemporal instability of ventricular repolarization. It has been revealed in many experimental and theoretical studies that the steeper the APD restitution slope, the greater the spatial heterogeneity of APD during premature excitation, leading to the perturbation of propagation through the formation of wavebreaks. The present study showed that the MAPD restitution slope in the bepridil-treated patients was significantly less steep than in the control patients in both the RVOT and RVA. This may ameliorate the dynamic instability of the ventricular repolarization during premature excitation. In line with this prediction, the S2-induced amplification of the $T_{\text{peak-end}}$ interval was markedly attenuated in the patients treated with bepridil; no significant difference was recognized in the $T_{\text{peak-end}}$ interval during the S2 stimulus between the 2 groups. This observation suggests that flattening of the MAPD restitution may counteract the bepridil-induced inhomogeneous prolongation of the MAPD in patients with no structural heart disease. The prolongation of the MAPD accompanied by the flattening of its restitution kinetics is a unique electropharmacological property of bepridil. It might be ascribed to the combined inhibition of I$_{K}$, I$_{Ks}$ and I$_{Ca,L}$ but further investigation will be required to substantiate this interpretation.

**Study Limitations**

There were several limitations to the present study. First,
the MAPs were recorded from the RV, but not from the LV in this clinical study. It was impossible to record the MAPs from the LV in 5 of the control patients and 3 of the bepridil-treated patients because the electrophysiological study was limited to the right side of the heart. Second, the MAPD restitution was examined using the standard S1–S2 protocol in order to evaluate the premature stimulation-induced perturbation of the ventricular repolarization. A dynamic pacing protocol, where the CL of the constant stimulation is shortened progressively, might be more appropriate for characterizing the action potential properties responsible for the transition from ventricular tachycardia to fibrillation. Third, the study included only patients with no structural heart disease. Bepridil-induced TdP has been reported to be more prevalent in patients with structural heart disease and in the presence of hypokalemia or marked bradycardia, conditions known to reduce the repolarization reserve and increase the spatial heterogeneity of ventricular repolarization. Under such pathologic conditions, bepridil would further enhance the heterogeneity of ventricular repolarization to a critical level for the induction of TdP. Unraveling the spatial and dynamic modification of the action potential properties by bepridil in human hearts under such pathological conditions will be a subject for further investigation.

Conclusions

Bepridil produces an inhomogeneous prolongation of the MAPDs, but flattens their restitution kinetics in the human ventricle. The former effect would favor the functional reentry predisposing to TdP, whereas the latter one would counteract that by reducing the dynamic instability of the repolarization.

References