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Effects of bepridil on ventricular depolarization and repolarization of rabbit isolated hearts with particular reference to its possible proarrhythmic properties

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1 Effects of bepridil on ventricular depolarization and repolarization sequences were examined in rabbit Langendorff-perfused hearts.

2 In distant bipolar electrograms (DBEs), bepridil, 10^{-6} M, caused a significant prolongation of QT intervals. At 10^{-5} M, the QT prolongation was further enhanced, and a significant prolongation of QRS duration was also observed. Polymorphous ventricular tachycardia was frequently induced by a single premature stimulus at the higher concentration.

3 In epicardial electrograms recorded through modified bipolar electrodes, bepridil, 10^{-6} M, prolonged the interval from the peak negative deflection of the QRS complex to the apex of the T wave (Q–aT), which corresponded to the intracellular action potential duration at 90% repolarization (APD_{90}). The Q–aT prolongation was larger in the base than in the apex, resulting in a marked distortion and dispersion of repolarization. The epicardial activation sequence was unaffected.

4 At 10^{-5} M bepridil, the dispersion of repolarization was much more enhanced by activation delay in the epicardial surface.

5 These findings suggest that bepridil causes regionally different lengthening of APD in ventricular muscle leading to an increase in temporal dispersion of repolarization, and that this dispersion may be inducive for re-entrant arrhythmias when accompanied by slow conduction at toxic doses.

Introduction

Bepridil is a relatively new compound having both antianginal and antiarrhythmic effects. The pharmacological profile of this substance is complex. Its potent vasodilating action may be mediated primarily by the inhibition of calcium influx through the cell membrane, as with other calcium antagonists currently available (Schwartz *et al.*, 1985; Flaim & Cummings, 1986). However, some intracellular mechanisms relating to the calcium modulator protein have also been proposed (Itoh *et al.*, 1984). Electrophysiological experiments on cardiac tissue have revealed that this substance inhibits both the fast sodium and the slow calcium channels (Vogel *et al.*, 1979; Labrid *et al.*, 1979; Anno *et al.*, 1984; Yatani *et al.*, 1985). Various changes in action potential duration induced by this drug have also been described (Kane & Winslow, 1980; Anno *et al.*, 1984; Kato & Singh, 1986; Winslow *et al.*, 1986).

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Clinical studies have shown that bepridil causes a significant increase in QT and corrected QT-intervals of the ECG (Duchene-Marullaz *et al.*, 1983; Flammang *et al.*, 1983; Somberg *et al.*, 1985; Singh *et al.*, 1985). It is well known that such QT prolongation by antiarrhythmic agents is associated with an increased likelihood of malignant ventricular tachyarrhythmias of polymorphous configuration or of a *Torsade de Pointes (T d P)* pattern (Krikler & Curry, 1979; McComb *et al.*, 1980; Keren *et al.*, 1981; Laakso *et al.*, 1981; Strasberg *et al.*, 1981; Chow *et al.*, 1984; Roden *et al.*, 1986). Some cases of *T d P* in patients treated with bepridil have also been described (Chabanier *et al.*, 1983; Leclercq *et al.*, 1983).

In the present study, we investigated the effects of bepridil on ventricular depolarization and repolarization sequences in rabbit isolated hearts, in order to elucidate the underlying mechanism of QT prolongation and its causative relationship to the possible proarrhythmic properties of this drug.

Methods

Rabbits (1.5–2.0 kg) were killed by a blow on the head, and the hearts were quickly removed. A cannula was inserted into the aorta for Langendorff perfusion, and the heart was perfused at a constant hydrostatic pressure (100 cmH_2O) with Krebs-Ringer solution gassed with 95% O_2 + 5% CO_2. The composition of the perfusate was as follows (mM): NaCl 120, KCl 4, $CaCl_2$ 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25.2 and glucose 5.8. The temperature of the perfusate was maintained at 32°C. The right atrium was incised, and the lower part of the A-V node was ligated with a fine silk thread to produce A-V block. The heart was entirely immersed in a tissue bath and constantly driven at 1.0 Hz from the proximal end of the His-bundle through a pair of contiguous bipolar electrodes made of stainless steel wires. To induce ventricular tachycardia (VT), a single premature stimulus (S2) was applied to the His-bundle after every 10th basic stimulus (S1) with a coupling interval 10 ms longer than the effective refractory period. Three or more successive nonstimulated ventricular excitations were defined as VT. Pulses used were 2 ms in duration and 1.2 times the diastolic threshold for basic stimuli and 4.0 times the value for premature stimuli. Distant bipolar electrograms (DBEs) were recorded through a pair of Ag-AgCl wire electrodes placed 1.0 cm away from the basal and apical sides of the heart.

When the sequence of ventricular depolarization and repolarization was examined, epicardial electrograms were recorded from 20 to 30 sites on the posterior surface of the ventricle with a pair of modified bipolar electrodes made of stainless steel wire having a diameter of 100 μm. The shorter reference lead of the electrodes was positioned 2 mm above the surface of the epicardium (Veenstra *et al.*, 1984). The signals were amplified with a time constant of 0.01 s. The interval from the initiation of a ventricular complex in DBE (reference) to the instant showing peak negative deflection of the QRS in each epicardial electrogram was defined as the activation time (AT). The interval from the peak negative deflection to the positive peak (apex) of the T wave in the epicardial electrogram (Q–aT) was also measured, and the algebraic sum of AT and Q–aT was defined as the repolarization time (RT).

In some experiments, intracellular and extracellular potentials were recorded simultaneously in order to verify their temporal relationship. The endocardial surface of the interventricular septum, rather than the epicardial surface, was used for these experiments because it allowed much more stable impalement of microelectrodes. The right ventricular free wall was removed to expose the endocardial surface of the septum. Cut-ends of coronary arteries were carefully ligated with fine threads so that effective perfusion was maintained in the remaining tissue. Intracellular action potentials were recorded through floating glass microelectrodes filled with 3 M KCl and having a resistance ranging from 10 to 20 MΩ. Extracellular potentials were recorded through modified bipolar electrodes as described above. Both recording sites were set as close as possible (within 0.3 mm).

Control measurements were performed after an equilibration period of 30 min. Then, the heart was perfused with test solutions containing bepridil at concentrations of 10^{-6} M and 10^{-5} M. The action of bepridil was tested 60 min after the drug application at each concentration.

Values were expressed as mean ± s.d. unless otherwise stated. Statistical analysis was performed by use of Student's paired t test, and significance was established at $P<0.05$. More details of each procedure are given in the Results.

Results

Change in distant bipolar electrogram and arrhythmia provocation

Effects of bepridil on the configuration of distant bipolar electrograms (DBEs) were examined in seven hearts constantly driven at 1.0 Hz (Table 1). Treatment with bepridil, 10^{-6} M, for 60 min resulted in a significant increase in QT interval, whereas QRS duration was unaffected. At the higher concentration of bepridil (10^{-5} M), a significant increase in QRS duration was also observed with a further prolongation of QT interval.

In untreated preparations, no VT was induced by the single premature stimulation protocol. After treatment with bepridil at 10^{-6} M, VT was induced by S2 in one of the seven hearts. In the presence of bepridil at 10^{-5} M, VT was induced in five of the seven hearts, and VT terminated spontaneously within 10 s in four of these cases, while the remaining one deteriorated into ventricular fibrillation (VF) (Table 1). VT induced under such conditions was, in most cases, composed of polymorphous QRS complexes.

Depolarization and repolarization sequence of the ventricle

Effects of bepridil on ventricular depolarization and repolarization were investigated more extensively by extracellular potential mapping with modified bipolar electrodes.

First, we examined the temporal relationship between extracellular and intracellular potentials by recording them simultaneously from various sites of the right endocardial surface of the interventricular septum. Intracellular potentials were recorded

Table 1 Effects of bepridil on the configuration of distant bipolar electrogram (DBE)

	Basic stimulation		*Premature*
	QRS (ms)	*QT* (ms)	*VT or VF* (cases)
Control	75 ± 13	460 ± 63	0/7
Bepridil (10^{-6} M)	79 ± 13	528 ± 50*	1/7
Bepridil (10^{-5} M)	133 ± 21*	547 ± 50*	5/7

Values are mean ± s.d ($n = 7$). *Significantly different from control values ($P < 0.01$).

through a glass microelectrode from a site as close as possible to the tip of the modified bipolar electrodes (Figure 1). The initial sharp negative deflection of QRS complex in the extracellular potential ($Ø_e$) correspond well with the upstroke phase of the intracellular action potential ($Ø_i$) while the positive peak (apex) of T wave did so with the terminal phase of action potential repolarization. This may indicate that action potential duration (APD) at the recording site can be estimated by measuring the interval from the initial sharp negative deflection of QRS complex to the apex of T wave (Q–aT) in the extracellular potentials. Figure 2 shows 21 pairs of data obtained from two hearts driven either at 1.0 or 2.0 Hz. There was a very good correlation between Q–aT and APD at 90% repolarization (APD_{90}) ($r = 0.98$).

Depolarization and repolarization sequences on the posterior epicardial surface of the ventricle were examined in seven hearts. Representative results are shown in Figure 3. In this heart, QRS duration and QT interval in DBE under control conditions were 72 ms and 440 ms, respectively. Epicardial activation proceeded from the apex to the base, with a maximum difference in activation time in the mapped area (ΔAT) of 13 ms. Q–aT of the epicardial electrograms was shorter in the base than in the apex with a maximum difference (Δ Q–aT) of 29 ms. Repolarization, consequently, proceeded from the base to the apex with a maximum difference in repolarization time (Δ RT) of 21 ms.

After treatment with bepridil, 10^{-6} M, for 60 min, the QT interval was prolonged to 512 ms, whereas the QRS duration was unaffected in DBE. The T wave was somewhat flattened, giving rise to a more rounded shape, but its polarity was unchanged. The epicardial activation sequence and Δ AT (14 ms) were similar to the control. Q–aT was prolonged throughout the whole mapped area, but this change was much more pronounced in the base than in the apex, resulting in an increase in Δ Q–aT to 34 ms. Because of this regionally different Q–aT change, the repolarization sequence was highly distorted, and proceeded from the

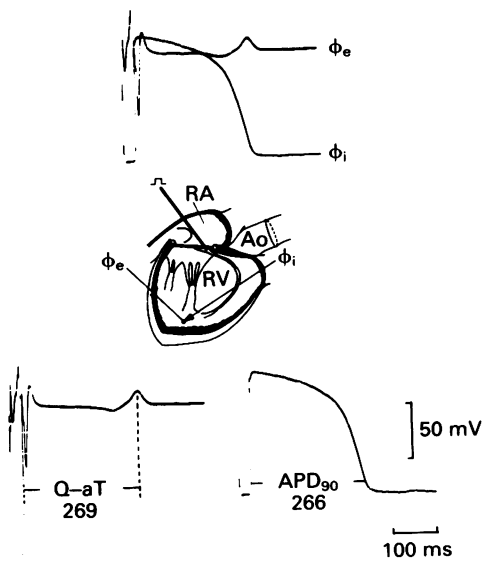

Figure 1 Simultaneous recordings of extracellular and intracellular potentials. The Q–aT of the extracellular potential and APD_{90} of the intracellular potential were 269 ms and 266 ms, respectively (lower panel). RA: right atrium; RV: right ventricle; Ao: aorta; $Ø_e$: extracellular potential; $Ø_i$: intracellular potential.

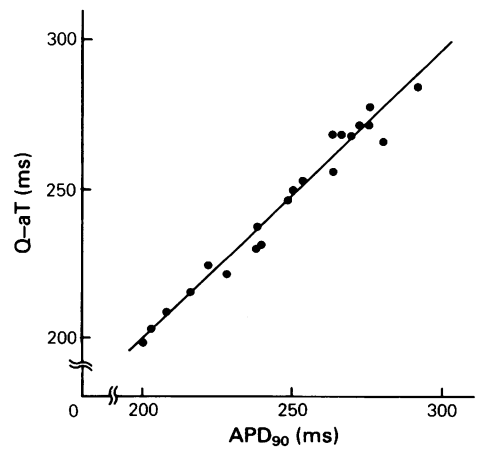

Figure 2 Correlation between Q–aT and action potential duration at 90% repolarization (APD_{90}). Twenty-one pairs of extracellular and intracellular potentials were obtained from two hearts driven at either 1.0 or 2.0 Hz. A good correlation was observed between the two ($r = 0.98$; $P < 0.001$).

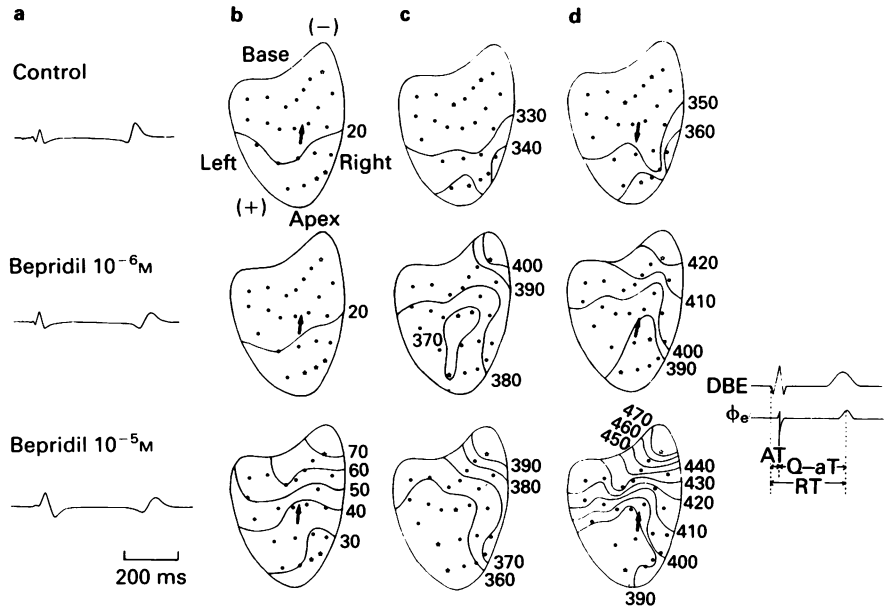

Figure 3 Effects of bepridil on depolarization and repolarization sequences on posterior ventricular surface. Distant bipolar electrograms (DBEs) (a), and maps of activation time (b), Q–aT interval (c) and repolarization time (d) in control and after treatment with bepridil at 10^{-6} M and 10^{-5} M are shown. Open and solid stars indicate the maximum and the minimum values for each map. Each arrow indicates the global direction of epicardial activation or repolarization sequence. (+) and (−) indicate sites and polarity of distant bipolar electrodes. See text for details.

apex to the base (a direction opposite to that of the control). Δ RT increased to 42 ms.

Bepridil, 10^{-5} M, caused a further prolongation of QT interval (550 ms) with a significant increase in QRS duration (120 ms) in DBE. Although AT was prolonged at all recording sites, with an increase in Δ AT to 44 ms, the global direction of epicardial activation sequence was the same as in the control (from apex to base). Q–aT in each electrogram was slightly shorter than the value at the lower concentration of bepridil (10^{-6} M). However, the pattern of the Q–aT map was similar to that at 10^{-6} M, with Δ Q–aT of 42 ms. As a result, ventricular repolarization proceeded from the apex to the base, with an appreciable increase of Δ RT to 86 ms.

Similar results were obtained in the remaining six hearts. Average values of measured parameters in all the seven hearts were as follows. Under control conditions, Δ AT was 13 ± 4 ms, Δ Q–aT was 29 ± 14 ms and Δ Rt was 26 ± 8 ms. After treatment with bepridil at 10^{-6} M, Δ AT was not affected (13 ± 6 ms), whereas Δ Q–aT and Δ RT increased significantly to 42 ± 11 ms ($P<0.01$) and to 54 ± 15 ms ($P<0.01$), respectively. At 10^{-5} M bepridil, Δ AT also increased significantly to 44 ± 4 ms ($P<0.01$ vs control). Δ Q–aT was 49 ± 14 ms ($P<0.01$ vs control), and Δ RT reached 92 ± 20 ms ($P<0.01$ vs control), a value more than three times that of the control.

Discussion

The present experiments on rabbit isolated hearts indicate that bepridil, 10^{-6} M, caused a significant prolongation of the QT interval with a flattening of the T wave in the distant bipolar electrograms (DBEs). The QRS duration was unaffected. These findings are consistent with clinical reports on ECG change (Duchene-Marullaz *et al.*, 1983; Flammang *et al.*, 1983) and suggest that bepridil at therapeutic concentrations lengthens ventricular repolarization without affecting the depolarization process. This has been confirmed by our mapping with modified bipolar electrodes on the posterior epicardial surface of ventricle. Thus, bepridil (10^{-6} M) prolonged the Q–aT interval corresponding to the action potential duration at 90% repolarization (APD_{90}) at all the recording sites. The Q–aT change was appreciably greater in the base than in the apex, resulting in marked distortion of the repolarization sequence; the repolarization proceeded in a direction opposite to that of control.

In previous *in vitro* experimental studies, there were some discrepancies in the bepridil-induced changes in APD of ventricular muscles. Kane & Winslow (1980) and Winslow *et al.* (1986) demonstrated that bepridil caused significant prolongation of APD_{90} in guinea-pig and rabbit papillary muscles. Kato & Singh (1986) also showed prolongation of APD_{90} in dog papillary muscles. On the other hand, Anno *et al.* (1984) demonstrated that APD_{90} of guinea-pig papillary muscles was not affected by bepridil. In guinea-pig isolated ventricular cells, Yatani *et al.* (1985) showed a marked shortening of APD by bepridil. Such discrepancies may be attributable to species differences or different experimental conditions. Our results for APD prolongation agree with those on rabbit papillary muscles.

The underlying mechanism for the regionally different APD prolongation of ventricular muscle is unknown. Winslow *et al.* (1986) have recently demonstrated that the bepridil-induced APD change is highly influenced by extracellular potassium. According to their experiments, % prolongation of APD_{90} by bepridil in rabbit papillary muscles was enhanced by several times when the K^+ concentration in the medium was lowered from 5.6 mM to 2.8 mM. In cardiac tissue, K^+ concentration in extracellular fluid just adjacent to the myocardial cell membrane is known to vary considerably because of the limited rate of diffusion in narrow spaces such as the intercellular cleft or transverse tubules (Sommer & Johnson, 1979). Myocardial cells in different sites of the ventricle might, therefore, be exposed to somewhat different K^+ concentrations leading to different responses to bepridil. Nevertheless, we cannot rule out other possibilities, such as regionally different membrane ionic conductances, and further studies are required to clarify the point.

Bepridil at 10^{-5} M, corresponding to several times higher concentration than the therapeutic plasma level, caused a significant prolongation of the QRS duration in DBEs in addition to a further prolongation of the QT interval. In concordance with the QRS change, an appreciable activation delay was observed in the epicardial mapping. This activation delay can be attributed to sodium channel inhibition by the drug. Anno *et al.* (1984) found that bepridil at concentrations above 5×10^{-6} M caused a dose-dependent decrease in the maximum upstroke velocity ($\dot{V}_{max}$) of action potentials in guinea-pig ventricular muscles. Similar $\dot{V}_{max}$ inhibition was shown in rabbit and canine cardiac tissues (Kato & Singh, 1986; Winslow *et al.*, 1986). Furthermore, in voltage-clamp experiments on neonatal rat ventricular cells, bepridil at above 10^{-6} M decreased the peak amplitude of the fast sodium inward current in a dose-dependent manner (Yatani *et al.*, 1985).

At 10^{-5} M bepridil, Q–aT in each epicardial electrogram and Δ Q–aT were more or less similar to those at 10^{-6} M. However, the repolarization sequence was further distorted due to the activation delay, and the Δ RT, a parameter indicating dispersion of ventricular repolarization, reached a value more than three times that of control. The high incidence of ventricular tachycardia (VT) in the presence of bepridil at 10^{-5} M (Table 1) can most likely be explained by this larger dispersion of repolarization, a condition known to set the stage for re-entry of excitation (Han & Moe, 1964; Marix *et al.*, 1977).

Allessie *et al.* (1976) demonstrated in their experiments, using rabbit isolated atria, that a certain degree of dispersion of repolarization is required to induce circus movement tachycardia by premature stimuli. Also, Kuo *et al.* (1983) showed in dog hearts that a critical level of dispersion in ventricular repolarization is necessary for the induction of arrhythmia by premature stimuli. The present results suggest that the critical level of dispersion in ventricular repolarization can be attained at high bepridil concentrations through a combination of regionally different APD prolongation and conduction delay.

$\dot{V}_{max}$ inhibition by bepridil is markedly enhanced by depolarization of the resting membrane potential (Anno *et al.*, 1984). It is quite possible that a similar proarrhythmic combination is induced by therapeutic use of this drug in hearts with various pathological conditions. Pharmacokinetic studies have shown that bepridil has low plasma clearance, probably due to its high protein binding, and a very long half-life (approximately 2 days) (Benet, 1985). Therefore, during clinical use of bepridil, frequent ECG monitoring is recommended. A significant prolongation of QRS duration accompanied by a long QT interval would be predictive of proarrhythmic properties of this drug.

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