Effects of Bepridil on Atrial Electrical Remodeling in Short-Term Rapid Pacing

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Introduction: Bepridil is a multi-ion channel blocker similar to amiodarone. Recent clinical studies have indicated that bepridil shows a favorable efficacy for the treatment of atrial fibrillation (AF). The purpose of this study is to evaluate the effectiveness of bepridil for electrical remodeling induced by rapid atrial stimulation particularly in the acute-phase.

Methods and Results: We studied 18 pigs subjected to right atrial appendage rapid pacing at 500 beats/min for 3 hours that were randomly assigned to the absence or presence of bepridil administration for 14 days. They were divided into 2 groups, an atrial pacing only group (PG; n = 10) and an atrial pacing plus bepridil group (PBG; n = 8). We measured the effective refractory period (ERP) at the right atrial free wall (RAFW), the right atrial appendage (RAA) and the left atrial free wall (LAFW), as well as the monophasic action potential duration at 90% (MAPD\textsubscript{90}) in RAA during the rapid pacing phase and recovery phase.

In the PG, the ERP decreased gradually at all atrial sites during the 3 hour phase of rapid pacing. In contrast, the shortening of the ERP was suppressed significantly at the RAFW and LAFW in the PBG. The MAPD\textsubscript{90} was also shortened by rapid atrial pacing in the PG. This shortening was suppressed significantly in the PBG.

We evaluated the effect of bepridil on the inducibility of AF during all time spans. The mean number of AF occurrences in the PBG was significantly fewer than in the PG. (2.1 ± 2.4 vs. 8.5 ± 7.0, p < 0.05)

Conclusions: Bepridil prevented the shortening of the ERP and MAPD\textsubscript{90} induced by rapid atrial pacing in the acute phase. The results of this study might explain the efficacy of bepridil for preventing the recurrence of paroxysmal AF.

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Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias and increases the risk of ischemic stroke.\textsuperscript{1) Previous studies have suggested that AF produces the electrophysiological remodeling which is characterized by shortening of the effective refractory period (ERP) of the atrium.\textsuperscript{2,3) It is known

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that electrophysiological remodeling plays an important role in inducibility and persistence of AF. Recent studies reported that statin, prednisone and amiodarone prevented electrical remodeling of the atrium on pacing-induced AF animal models.4-6)

Bepridil hydrochloride has multiple ion-channel blocking effects similar to amiodarone and is useful for persistent AF conversion and maintenance of sinus rhythm.7) It has been reported to suppress atrial ERP shortening in continuous rapid pacing during the subacute to chronic phase. The purpose of this study is to evaluate the effectiveness of bepridil for electrical remodeling induced by rapid atrial stimulation in the acute-phase.

**Methods**

All experiments were performed in accordance with guidelines for animal research in our institute. Eighteen female pigs weighting 26.6 ± 2.9 kg were randomly divided into 2 groups, an atrial pacing only group (PG; n = 10) and an atrial pacing plus bepridil group (PBG; n = 8). The pigs in the PBG were administered oral bepridil 200 mg/day starting 2 weeks before pacing.

All pigs were sedated with intravascular ketamine hydrochloride and anesthetized with intravenous sodium pentobarbital. Room air was mechanically ventilated.

After midline thoracotomy, pairs of needle electrodes were attached to the right atrial free wall (RAFW) and left atrial free wall (LAFW). To record the monophasic action potential duration at 90% (MAPD90), a contact electrode catheter (MAP catheter 1675P Boston Scientific) was inserted into the right atrial appendage (RAA) through the right internal jugular vein. For continuous atrial rapid pacing, a screw-in pacing lead connected to a generator (customized Thera SR, Medtronic) was fixed on the epicardium of the right atrial appendage (Figure 1). About one hour after the induction of anesthesia, baseline electrophysiological study was performed. The output for stimulation was set at twice the diastolic threshold. Atrial ERP was measured at the RAFW, LAFW and RAA by applying eight basic stimuli (S1) at cycle length of 400 ms followed by one premature stimulus (S2). The S2 coupling interval was shortened in 5-ms steps and the atrial ERP was defined as the longest S1-S2 interval that failed to capture the atria. The MAPD90 was measured at a cycle length of 400 ms.

In each group, rapid atrial pacing at 500 beats per minute was continued for 180 minutes. Every 30 minutes an electrophysiological study was repeated to record the atrial ERP and MAPD90 changes. To measure the AF inducibility we counted the number of AF occurrences during extra-stimulation. AF was defined as a rapid irregular electrogram lasting >1 second.

**Statistical Analysis**

All data were presented as a mean ± SD. Differences between groups were evaluated by paired Student’s t-test. A two-tailed P value less than 0.05 was taken to indicate statistical significance. ANOVA for repeated measures was used to compare the effects of rapid atrial pacing in each region.

![Figure 1 Schematic positions of the atrial electrodes.](image-url)
Results

We measured PR and RR intervals, QRS duration and QT, as well as the QTc interval in ECGs at baseline. Although the PR intervals and QRS duration were not significantly different among the two groups, the RR intervals, QT, and QTc interval were significantly prolonged in the PBG ($499.4 \pm 42.5$ vs $618.1 \pm 116.5$ ms; $P < 0.05$, $280.0 \pm 28.2$ vs $359.4 \pm 41.8$ ms, $395.8 \pm 34.4$ vs $465.0 \pm 34.3$ ms; $P < 0.01$). There were no adverse effects including torsade de pointes (Tdp) due to QT intervals prolongation.

In the PBG, the mean plasma concentration of bepridil was $193.4 \pm 265.7$ ng/ml.

Effects of Bepridil on Atrial ERP and MAPD$_{90}$

Figure 2 compares the regional ERPs before atrial rapid pacing. The ERP was longer in the PBG than the PG, but only the RAA showed a significant increase in PBG (PG, $194.8 \pm 27.5$ ms; PBG $227.3 \pm 22.6$ ms; $P < 0.05$). Serial ERP changes during atrial rapid pacing and recovery period are shown in Figure 3(A–C). In both groups, the atrial ERP decreased gradually by rapid pacing temporally and recovered eventually to nearly the pre-rapid pacing state in the recovery period.

Bepridil prolonged atrial ERP in all time courses significantly in the RAFW and LAFW ($P < 0.05$).

Figure 4 shows the effects of rapid pacing and bepridil after 180 minutes on the ERP in different regions. Rapid pacing decreased atrial ERPs in all regions significantly. However, in the presence of bepridil, atrial ERPs were significantly prolonged.

Similar temporal changes were observed in MAPD$_{90}$ (Figure 5). MAPD$_{90}$ values were shortened.
During atrial rapid pacing and they recovered immediately after stopping pacing in both groups. In the presence of bepridil, the values of MAPD90 remained significantly longer (P < 0.01).

AF Inducibility

Figure 6 shows the incidence of AF in both groups in all time spans. The mean number of AF occurrences in the PBG was significantly fewer than in the PG. (2.1 ± 2.4 vs. 8.5 ± 7.0, p < 0.05)

Discussion

Major Findings

The major finding of this study is that bepridil pretreatment attenuated the shortening of ERP or MAPD90 values caused by short-term atrial rapid pacing in the acute phase. This study shows rapid atrial pacing leads to electrical remodeling that occurs inhomogeneously.

Mechanisms of Atrial Electrical Remodeling in the Acute Phase

Many studies have reported the atrial electrophysiological remodeling caused by rapid pacing in animal AF models during various periods. We found that rapid pacing increases the inducibility of AF and shortening of the ERP and MAPD90 even in the acute phase and bepridil attenuated these phenomena.

It has been well established that Ca2+ currents play an important role in atrial electrical remodeling. The shortening of atrial ERP due to tachycardia was considered to be the result of a significant reduction of the density of L-type Ca2+ current (ICaL) in the acute phase. The ICaL blocker verapamil and diltiazem prevent this alteration. Whereas the selective T-type Ca2+ current (ICaT) blocker mibebradil reduces atrial remodeling in the mid-to-late phase. According to some studies, bepridil blocks both ICaL and ICaT. Especially, bepridil has a concentration-dependent strong ICaL blocking effect. Nishida et al. reported the efficacy of bepridil against the expression of L-type calcium channel α1c messenger ribonucleic acid (mRNA) after 6 weeks of rapid atrial pacing. α1c mRNA expression was decreased in only the rapid pacing group. By using bepridil, it was maintained signifi-
cantly higher than in the pacing only group. These results may support the view that the blocking effects of both \( I_{\text{Cal}} \) and \( I_{\text{Ct}} \) of bepridil prevent the atrial electrophysiological remodeling caused by rapid pacing in the acute to even the mid phase.

Bepridil blocks also the slow components of multiple \( K^+ \) currents such as the ultrarapid \( (I_{\text{kur}}) \), rapid \( (I_{\text{kR}}) \), and slow delayed rectifier current \( (I_{\text{ks}}) \). 
The \( I_{\text{kur}} \) was specifically blocked by bepridil, concentration-dependent, but not amiodarone. Yamashita et al. reported that the short-term rapid atrial pacing could increase transiently \( K_v1.5 \) gene expression encodes \( I_{\text{kur}} \). Accordingly, bepridil may prevent electrical remodeling to suppress this phenomenon. Furthermore, suppressing not only \( I_{\text{kur}} \) but also \( I_{\text{kR}} \), bepridil may force atrial action potential prolongation and display anti-arrhythmic effects.

Thus, these ion-channels blocking effects of bepridil may also be closely related to the prevention of electrical remodeling in clinical situations.

**Regional Effects of Bepridil**

We evaluated the regional differences in the effect of bepridil and rapid pacing on the ERP. Although there is a significant prolongation of the ERP in only the RAA before rapid pacing by bepridil, it suppressed the rapid-pacing-induced ERP shortening in the RAFW and LAFW more than in the RAA. These results suggest that the effect of bepridil and ERP shortening induced by rapid pacing was regionally heterogeneous. Fukaya et al. reported that the mRNA downregulation of L-type \( \text{Ca}^{2+} \) channel and SCN5A caused by rapid atrial stimulation in dogs were negated by bepridil in the RA; but not in the LA.

Although the mechanism of this heterogeneity was unclear, the regional differences in the mechanical stretch during rapid pacing may play an important role. Fareh et al. reported that tachycardia-induced ERP remodeling that plays an important role in increasing atrial vulnerability to AF is spatially nonuniform. Nevertheless, bepridil eventually suppressed the inducibility and incidence of AF in this rapid pacing pig model.

**Study Limitations**

The first limitation is that we did not adjust the ventricular response during atrial rapid pacing. Therefore rapid ventricular response may affect the hemodynamics and electrophysiological characteristics of the atrium. The second limitation is that we could not evaluate the hemodynamic factors such as systemic blood pressure and atrial pressure. Lastly, the operation under pentobarbital anesthesia and bleeding modified the autonomic nerve tone in the experimental model.

**Conclusion**

Bepridil prevented the shortening of the ERP and \( \text{MAPD}_{90} \) induced by rapid atrial pacing and subsequent incidence of AF in the acute phase. The results of this study might explain the efficacy of bepridil for preventing the recurrence of paroxysmal AF.

**References**

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