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Original article

Bepridil enhances aprindine-induced prolongation of atrial effective refractory period in a canine atrial rapid pacing model

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ABSTRACT

Background: Bepridil in combination with aprindine could restore sinus rhythm in patients with persistent atrial fibrillation (AF). The present study aimed to investigate the electrophysiological mechanisms of the combined effects of bepridil and aprindine.
Methods: Subjects consisted of 6 dogs without and 6 dogs with atrial rapid pacing (ARP) carried out at 400 bpm for 2 weeks. Bepridil was administered for 1 week in both groups (ARP dogs were administered bepridil in the second week). The electrophysiological effects of the intravenous administration of aprindine (1 mg/kg) were evaluated before and after the administration of bepridil.
Results: In non-paced dogs, the atrial effective refractory period (AERP) became longer after the administration of bepridil (from 151 ± 10 ms to 170 ± 7 ms, $p < 0.05$); however, no additional AERP prolongation was observed after the acute administration of aprindine. In ARP dogs, the AERP shortened with ARP for a week, and tended to lengthen after the administration of bepridil (from 93 ± 5 ms to 118 ± 9 ms, $p = 0.08$). In these dogs, the acute aprindine administration did not prolong the AERP before the administration of bepridil, although it did after the administration of bepridil (from 118 ± 9 ms to 142 ± 8 ms, $p < 0.01$). AF duration did not change after the administration of bepridil, although it shortened significantly after the additional administration of aprindine (from 2.2 ± 0.3 s to 1.4 ± 0.8 s, $p < 0.05$).
Conclusions: Bepridil enhances the effect of aprindine for the prevention of AF by reversing atrial electrical remodeling.

Introduction

The number of patients with atrial fibrillation (AF) is increasing, and AF is now the most common arrhythmia seen in clinical practice [1]. Growing evidence has suggested the efficacy of catheter ablation for AF [2]; however, pharmacotherapy remains an important treatment option for AF.

If AF is maintained, electrical remodeling develops to increase the stability [3]. In the process of electrical remodeling, sodium current (I_{Na}) decreases due to the downregulation of the underlying sodium channel α-subunit expression [4]. Accordingly, sodium channel blockers are sometimes ineffective in terminating persistent AF. In this situation, potassium channel blockers are sometimes effective. Bepridil, a multichannel blocker of rapid, slow, and ultrarapid delayed rectifier potassium currents (I_{Kr}, I_{Ks}, and I_{Kur}, respectively) [5,6], sodium current [7], and L- and T-type calcium currents ($I_{Ca,L}$ and $I_{Ca,T}$, respectively) [8,9], is effective in terminating drug-refractory, persistent AF [10–12]. Moreover, the additional administration of a sodium channel blocker, aprindine, increases the success rate of sinus conversion when comparing to patients with bepridil alone [11,12].

The mechanisms of the combined effects of bepridil and aprindine remain unclear. In the present study, the combined effects of bepridil and aprindine on atrial remodeling and AF development were examined using a canine atrial rapid pacing (ARP) model with preserved atrioventricular conduction that develops concomitant tachycardia-induced ventricular dysfunction

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[13]. In this model, both atrial electrical and structural remodeling were observed [14–16].

Methods

Experimental design

The investigation conformed to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication No. 85-23, revised 1996). The procedures were approved by the Animal Research Ethics Committee of the University of Toyama. Twelve beagles (Sankyo Laboratory, Tokyo, Japan) of either sex, weighing 9–11 kg, were subjects in the present study. First, the combined electrophysiological effects of bepridil and aprindine were determined in 6 non-paced dogs (Fig. 1, protocol 1). Electrophysiological study (EPS) was performed before and after the oral administration of bepridil (100 mg/day) for 1 week. Second, the combined effects of bepridil and aprindine were determined in 6 ARP dogs (Fig. 1, protocol 2). ARP was performed for 2 weeks, and bepridil was administered for the last week. EPS was performed at baseline, and after 1 week and 2 weeks of ARP. In each EPS, electrophysiological properties were determined before and after the intravenous administration of aprindine (1 mg/kg).

Animal preparation

ARP dogs were implanted with an atrial pacemaker, as previously described [14–16]. Dogs were anesthetized with ketamine (5.0 mg/kg, im), isoflurane (induction, 4 vol%; maintenance, 2 vol%), nitrous oxide (1.5 L/min), and oxygen (3.0 L/min), and ventilated mechanically with a volume-cycled respirator (607E, Harvard Apparatus, Millis, MA, USA). The left femoral vein was cannulated to allow infusion of 0.9% saline for replacement of spontaneous fluid losses. After right lateral thoracotomy at the fourth intercostal space, a tetrapolar electrode (2 mm interelectrode distance, ON202-020, Unique Medical, Osaka, Japan) was sewn onto the epicardial surface of the right atrium (RA) for stimulation and recording during serial EPS. The electrode lead was tunneled subcutaneously to the inter-scapular area and exteriorized. A screw-in bipolar electrode (CapSureFix 5068, Medtronic, Minneapolis, MN, USA) was inserted via the right femoral vein, fixed to the RA appendage, and then connected to an atrial pacemaker (SIP 501, Star Medical, Tokyo, Japan) in a subcutaneous pocket created in the abdomen. Atrioventricular ablation was not performed, and atrioventricular conduction was preserved. After recovering from anesthesia, the dogs were closely monitored in an observation room for one day. They were then moved to a chronic care facility and placed on a 5-day course of ampicillin sodium and streptomycin sulfate. After a seven-day period of recovery from pacemaker implantation, the atrial pacemaker was programmed to pace the atrium at a cycle length of 150 ms (400 bpm).

Electrophysiological study

Dogs were anesthetized and ventilated in the same manner as in the initial surgery. In non-paced dogs, stimulation and recording were performed using electrode catheters inserted into the RA and the right ventricle via the right jugular vein. In ARP dogs, the atrial pacemaker was deactivated 30 min before starting each EPS, and stimulation and recording were performed using the implanted RA tetrapolar electrode. A cardiac stimulator (SEC-2102, Nihon Kohden, Tokyo, Japan) was used to deliver square wave pulses of 1 ms in duration. Surface electrocardiogram, RA electrogram, and right ventricular electrogram were monitored using an oscilloscope (VC-11, Nihon Kohden) and recorded on a thermal recorder (RTA-1200M, Nihon Kohden) at a paper speed of 100 mm/s. These data were also stored in a digital data recorder (RD-130TE, TEAC, Tokyo, Japan) for further analyses. P-wave duration, QRS duration, and QT interval were measured in lead II. The atrial effective refractory period (AERP) and ventricular effective refractory period (VERP) (in non-paced dogs only) were measured at the RA and the right ventricle with a train of 10 basic stimuli (S1) followed by a premature stimulus (S2) at twice the diastolic threshold. Basic cycle lengths (BCLs) were 400, 350, 300, 250, and 200 ms for AERP, and 300 and 200 ms for VERP. The coupling interval of S2 was shortened by a 5 ms step. AERP and VERP were defined as the maximum S1–S2 interval resulting in no atrial and ventricular response, respectively. AF induction was performed with atrial burst pacing of 20 stimuli at

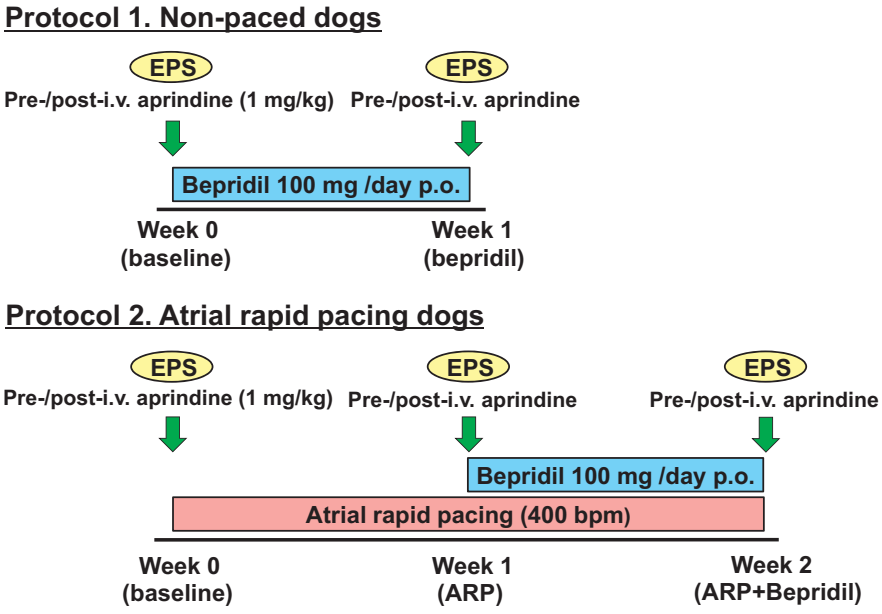

Fig. 1. Time course of the experiment. Protocol 1. In the experiment with non-paced dogs, bepridil was orally administered for 1 week. EPS was performed before and after the administration of bepridil. Protocol 2. In the experiment with ARP dogs, ARP was performed for 2 weeks, and bepridil was started after 1 week of ARP and continued thereafter. EPS was performed each week. The electrophysiological effects of acute intravenous administration were evaluated. ARP, atrial rapid pacing; EPS, electrophysiological study.