**d,l–Sotalol Reverses Abbreviated Atrial Refractoriness and Prevents Promotion of Atrial Fibrillation in a Canine Model With Left Ventricular Dysfunction Induced by Atrial Tachypacing**

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**Background:** This study evaluated antiarrhythmic effects of d,l–sotalol in a canine atrial fibrillation (AF) model with left ventricular dysfunction.

**Methods and Results:** Thirteen beagles (Sotalol group n=7 and Control group n=6) were subjected to atrial tachypacing (ATP) (400 beats/min) with intact atrioventricular conduction for 4 weeks. Oral d,l–sotalol (2 mg/kg) was administered 1 week after starting ATP and continued throughout the experiment. One week after starting ATP, atrial effective refractory periods (AERPs) were shortened in both groups. However, d,l–sotalol treatment gradually prolonged AERP, resulting in a significant prolongation of AERP compared with the Control group at 4 weeks (Control 76±4 and Sotalol 126±5 ms, P<0.01). d,l–Sotalol treatment showed lower AF inducibility and shorter AF duration at 4 weeks. In the control group, expressions of L-type Ca\(^{2+}\) channel α1c and Kv4.3 mRNA were downregulated by 46.2% and 43.0%, respectively, after 4 weeks of ATP; d,l–sotalol treatment did not affect these changes.

**Conclusions:** d,l–Sotalol treatment prolonged AERP, even after atrial electrical remodeling had developed, and prevented AF perpetuation without affecting downregulated expression of L-type Ca\(^{2+}\) channel α1c and Kv4.3 mRNA in an ATP-induced canine AF model. (Circ J 2009; 73: 1820–1828)

**Key Words:** Atrial fibrillation; d,l–sotalol; Electrical remodeling; L-type Ca\(^{2+}\) channel; LV dysfunction

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Atrial fibrillation (AF) is the most common sustained arrhythmia found in clinical practice. However, the pharmacological treatment of AF remains challenging because atrial tachyarrhythmias alter atrial electrophysiological properties to promote AF and attenuate the efficacy of antiarrhythmic drugs. This process is termed electrical remodeling, which consists of changes in the ionic current densities of L-type Ca\(^{2+}\) current, several K\(^{+}\) currents and Na\(^{+}\) current.

In a canine model of atrial tachypacing (ATP) with controlled ventricular rate, amiodarone prevented L-type Ca\(^{2+}\) channel downregulation and reversed pacing-induced shortening of the atrial effective refractory period (AERP) and AF promotion. In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), amiodarone was found to be more effective than d,l-sotalol for sinus maintenance, but for the pharmacological conversion of persistent AF, d,l–sotalol and amiodarone were equally effective on day 28 (d,l–sotalol 24.2%, amiodarone 27.1%). It is possible that d,l–sotalol could also reverse atrial electrical remodeling. In addition to its IKr blocking properties, d,l–sotalol has a β-adrenoceptor blocking effect and clinical studies have shown that chronic β blockade is associated with a reduction in atrial transient outward K\(^{+}\) current (Ito) density, thereby resulting in a prolongation of AERP. Kv4.3 mRNA is a putative gene encoding Ito. Hence, we evaluated the effects of d,l–sotalol on the atrial remodeling using a canine ATP model with preserved atrioventricular (AV) conduction and determined L-type Ca\(^{2+}\) channel α1c and Kv4.3 mRNA expression. In the present study, the AV block was not made before starting ATP because most patients with AF have intact AV conduction, which is sometimes associated with tachycardia-induced left ventricular (LV) dysfunction.

**Methods**

See Figure 1 for the time course of the study. Thirteen beagles (Sankyo Laboratory, Japan) weighing 8–12 kg were subjected to ATP for 4 weeks. Six dogs were paced for 4 weeks while receiving a placebo (Control group). The other 7 dogs were paced for 4 weeks while receiving d,l–sotalol orally (2 mg·kg\(^{-1}\)·day\(^{-1}\), Sotalol group). This dose of d,l–sotalol was selected to avoid the effects on AV nodal conduction and LV function. To mimic the clinical setting, either placebo or d,l–sotalol were administered 1 week after...
starting ATP and continued throughout the experiment. Another 5 dogs served as the Sham group for histological and biochemical analyses. Although they were instrumented in a similar manner to the other groups of dogs, their atrial pacemakers were not activated.

### Animal Preparation

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). All the dogs were anesthetized with ketamine (5.0 mg/kg, im) and isoflurane (induction, 4vol%; maintenance, 2vol%); nitrous oxide (1.5 L/min), and oxygen (3 L/min). They were ventilated via an endotracheal tube connected to a volume-cycled respirator (607E, Harvard Apparatus, Millis, MA, USA). A left femoral vein was cannulated to infuse 0.9% saline for replacement of spontaneous fluid losses. After the chest was opened through 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 atrial appendage (RAA) for electrophysiological study (EPS). The electrode lead was tunneled subcutaneously to the neck and exteriorized. A screw-in bipolar electrode (CapSureFix 5068, Medtronic, Minneapolis, MN, USA) was intravenously inserted from the right femoral vein and fixed to the RAA. It was connected to an atrial pacemaker (SIP 501, Star Medical, Tokyo, Japan) implanted epicardially to the anterior right atrial myocardium. During surgery, atrial conduction was preserved in the present study.

Another 5 dogs served as the Sham group for histological and biochemical analyses. Although they were instrumented in a similar manner to the other groups of dogs, their atrial pacemakers were not activated.

### EPS

After 7 days of recovery, a control EPS was performed using exposed subcutaneous electrode, and then the atrial pacemaker was programmed to pace the atrium at cycle lengths of 150–110 ms producing 1:1 atrial capture. A transesophageal electrode lead was inserted to record the left atrial (LA) electrogram. After confirming 1:1 atrial capture, the atrial pacemaker was deactivated and AERP, inducibility of AF, duration of induced AF, and QTc at a 400-ms cycle length were evaluated every one week thereafter. On each study day, the same anesthesia protocol in the initial surgery was used. A cardiac stimulator (SEC-2102, Nihon Kohden, Tokyo, Japan) was used to deliver square wave impulses of 1 ms duration. Surface electrocardiogram (ECG) lead II, atrial ECG and a transesophageal LA ECG were monitored with an oscilloscope (VC-11, Nihon Kohden, Tokyo, Japan) and also recorded simultaneously on a thermal recorder (RTA-1200M, Nihon Kohden, Tokyo, Japan) at a paper speed of 100 mm/s. They were stored in a digital data recorder (RD-130TE, TEAC, Tokyo, Japan) for further analyses.

AERPs were measured at the RAA with a train of 10 basic stimuli (S1) followed by a premature stimulus (S2) twice the diastolic threshold. Basic cycle lengths (BCLs) were 400, 350, 300, 250, 200 and 150 ms. The coupling interval of S2 was shortened in a 5-ms step and AERP was defined as the maximum S1–S2 interval resulting in no atrial response. AF inducibility was defined as the percentage of induced-AF episodes during 10 episodes of atrial burst pacing of 20 stimuli at the shortest cycle length producing 1:1 atrial capture. AF was defined as irregular, repetitive atrial responses lasting more than 1.0 s. Prolonged AF (>30 min) was terminated by direct current electrical cardioversion. If prolonged AF was induced twice, no further AF induction was performed. For each dog, AF durations were represented by the mean and longest duration of induced AF episodes.

AF cycle length (AFCL) was determined using spectral analyses of the fibrillation waves as reported in our previous study. Briefly, the right atrial (RA) ECG from the implanted epicardial electrode was digitally stored on a microcomputer (Value Star NX, NEC, Tokyo, Japan) at a sampling rate of 1 kHz. Frequency analysis of the stored electrograms involved three steps, including bandpass filtering, application of a Hamming window and a 4,096-point fast Fourier transformation. Power spectra were quantified by measuring the peak frequency signal with the maximum magnitude derived from each epoch. The peak frequency of the spectrum in the 5–20 Hz range was converted to a cycle length (cycle length in ms = 1,000/frequency) that was labeled AFCL. When AF was not sustained long enough for spectral analyses, AFCL was measured manually by counting the number of the electrograms present in the trace over 5–10 s and then dividing the duration in ms by the number of electrograms.

### Echocardiographic Measurements

Two-dimensional parasternal and trans-esophageal echocardiography (SSA-260A, Toshiba, Tokyo, Japan) was performed...
performed. Time course of changes in the LV end-diastolic dimension and LV end-systolic dimension in the parasternal long axis view and the LA area in the 4-chamber view were determined every week. Each examination was performed in sinus rhythm with the pacemaker off. LV end-diastolic and end-systolic volumes were measured using Teichholz’s method. LV ejection fraction (LVEF) was calculated as the difference between both volumes divided by LV end-diastolic volume.

Histological Examination
At the end of the experiments, all animals including the 5 sham dogs were euthanized by venesection under deep anesthesia induced by intravenous injection of an overdose of sodium pentobarbital. Samples were obtained from the RAA and the RA free wall. Longitudinal and transverse sections of each block were made. Sections were immersed in 10% neutral-buffered formalin and paraffin blocks were sliced at 5-μm thickness and stained with Masson’s trichrome.

The microscopic images were scanned into a personal computer and quantitatively analyzed with a specific software package (VH Analyzer, Keyence, Osaka, Japan). Connective tissues were quantified on the basis of a color discrimination algorithm that was manually verified; the result was expressed as a percentage of the reference tissue area. Blood vessels and perivascular interstitial cells were excluded from the connective tissue quantification.

Ribonucleic Acid (RNA) Preparation and Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR)
A sample of tissue weighing 0.3–0.5 g was obtained from the RAA and the RA free wall. After excision, the tissue was immediately snap-frozen in liquid nitrogen and stored at −80°C. Total RNA was extracted from individual samples with the use of ISOGEN (Nippon gene, Tokyo, Japan) according to the manufacturer’s instructions. Complementary DNA (cDNA) was synthesized from 3μg of the total RNA with a High Capacity RNA-to-cDNA kit (Applied Biosystems, Foster City, CA, USA) in a final volume of 20μl. The mRNA levels of the ion-channel-related molecules (L-type Ca\(^{2+}\) channel and Kv4.3) were evaluated using quantitative real-time RT-PCR.

For L-type Ca\(^{2+}\) channel evaluation, real-time RT-PCR was performed with a TaqMan technology using the primers (sense, GGGCATCCCGACCCTGT; TaqMan probe, TGGAGCCTTCATCAAGTCCTTCCAGGC; antisense CAGAAGAGCCACGTAAAGCCAG). As an internal control, the level of 18S ribosomal RNA was also evaluated using the primer pair (sense, CGATGAGGCCCAGGCAA; anti-
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The thermal cycling conditions were as follows: 1 min at 50°C for the initial step, 10 min at 95°C for deactivation, 45 cycles of 15 s at 94°C for denaturation, and 1 min at 60°C for annealing and extension. For the standard curve, the mixture of all samples was concluded. The expression level of target gene was evaluated using the ratio of target mRNA to internal control mRNA.

Statistical Analysis
All values are expressed as mean±SE. An unpaired t-test and a Mann–Whitney U-test were used to evaluate the significance of difference between the 2 groups. Time series data were analyzed using repeated analysis of variance (ANOVA) with a Student–Newman–Keuls test. Statistical comparisons of multiple groups were obtained using ANOVA with Fisher’s protected least significant difference. A P-value<0.05 was considered statistically significant.

Results

Changes in Electrophysiological Variables
In the Control group, AERP decreased at each BCL rapidly at 1 week and slowly thereafter throughout the experiment (Figure 2A). The rate adaptation of AERP disappeared in response to rapid atrial pacing at 1 week in both groups (Figure 2B, C). In the Sotalol group, AERP also decreased rapidly at 1 week, but the subsequent administration of d,l–sotalol gradually prolonged AERP, resulting in a significant AERP prolongation at 3 and 4 weeks, respectively (Figure 2A). In addition, AERPs were greater in the Sotalol group than in the Control group at 2–4 weeks (Figure 2A).

In the Control group, the QTc interval did not change throughout the experiment. The Sotalol group showed QTc prolongation, resulting in a significant QTc prolongation when compared with the Control group at 2–4 weeks (Figure 2D). In contrast to the time course of AERP changes, rapid prolongation of QTc interval by d,l–sotalol appeared earlier at 2 weeks, and remained constant until 4 weeks. There was no difference in the time course of plasma d,l–sotalol levels in the Sotalol group (2 weeks, 0.48±0.13 μg/ml; 3 weeks, 0.62±0.12 μg/ml; 4 weeks, 0.65±0.11 μg/ml, P=0.45).

Induction of AF
Changes in the mean and the longest AF durations, AFCL and AF inducibility are summarized in Figure 3. The mean and the longest AF durations did not differ between the 2 groups at 1 week, but they continued to increase thereafter in the Control group (Figures 3A, B). In contrast, d,l–sotalol administration inhibited AF perpetuation in the Sotalol group. As a result, the mean and longest AF durations became shorter in the Sotalol group than in the Control group at 3 and 4 weeks, respectively.

AFCL at 1 week did not differ between the 2 groups (Figure 3C). In the Sotalol group, AFCL was gradually prolonged after d,l–sotalol administration and became longer than that in the Control group at 2, 3, and 4 weeks. In the Control group, AF inducibility continued to increase throughout the experiment (Figure 3D). However, d,l–sotalol treatment prevented AF inducibility and became significantly lower when compared with the Control group at 3 and 4 weeks.

Representative examples of atrial electrograms and spec-
Figure 4. Representative examples of atrial electrograms and spectral analyses of atrial fibrillation (AF) induced at 4 weeks. AF was induced after burst pacing in the Control group (A) and the Sotalol group (B). Eso, esophageal lead; RAA, right atrial appendage lead; II, surface electrocardiogram lead II; AFCL, atrial fibrillation cycle length.

Figure 5. Representative echocardiographic recordings and 2 variables are shown. (A) Left ventricular (Upper panel) and left atrial echocardiogram (Lower panel) at baseline and 4 weeks in the Control group (Left) and the Sotalol group (Right). (B, C) Time course of changes in left ventricular ejection fraction (LVEF) and left atrial (LA) area did not differ between the 2 groups throughout the experiment. *P<0.01 vs baseline, **P<0.05 vs baseline.
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Central analyses of fibrillation waves are shown in Figure 4. In the Control group (Figure 4A), AF was sustained for 188 s and AFCL was short (102 ms) at 4 weeks, whereas in the Sotalol group (Figure 4B), AF was sustained for only 2.9 s and AFCL was prolonged to 142 ms at 4 weeks.

**Changes in Echocardiographic Findings**
Representative echocardiograms are shown in Figure 5A. In both groups, LVEF decreased rapidly at 1 week, and then remained constant until 4 weeks of pacing when compared with baseline. The degree of reduction in LVEF did not differ between the 2 groups throughout the experiment (Figure 5B). The LA area continued to enlarge throughout the experiment, and became significantly larger at 2, 3 and 4 weeks of pacing, compared with baseline in both groups (Figure 5C). The time course of body weight did not change in both groups, and the body weight did not differ between the 2 groups throughout the experiment (at 4 weeks, Control 9.8±0.8 kg and Sotalol 9.4±1.0 kg).

**Ventricular Response Rates**
Because the AV block was not produced in this model, the ventricular rate was dependent on AV nodal conduction properties. Neither the mean ventricular rate during ATP and sinus rhythm nor the shortest pacing cycle length, which exhibited 1:1 conduction to the ventricle, were affected by d,l–sotalol administration (Table).

**Histological Findings and Inter-Atrial Conduction Time**
Figure 6 shows representative examples of the atrial tissue fibrosis in the RA free wall at the end of the study period (Figure 6A). Interstitial fibrosis was increased in both the Control and Sotalol groups when compared with the Sham group (Figure 6B). Inter-atrial conduction time at a BCL of 200 ms continued to prolong, and became longer at 2, 3 and 4 weeks of pacing when compared with baseline in both groups (Figure 6C). d,l–Sotalol did not affect either the interstitial fibrosis or the inter-atrial conduction time.

**Table. Time Course of Ventricular Rate (beats/min)**

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<th>Control</th>
<th>Sotalol</th>
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<tr>
<td>During sinus rhythm</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>124±11</td>
<td>131±4</td>
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<tr>
<td>1 week</td>
<td>124±7</td>
<td>142±9</td>
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<tr>
<td>2 week</td>
<td>123±8</td>
<td>120±5</td>
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<tr>
<td>3 week</td>
<td>120±9</td>
<td>128±13</td>
</tr>
<tr>
<td>4 week</td>
<td>152±12</td>
<td>120±8</td>
</tr>
<tr>
<td>During atrial pacing</td>
<td></td>
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<tr>
<td>1 week</td>
<td>192±18</td>
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<tr>
<td>4 week</td>
<td>215±21</td>
<td>227±34</td>
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1:1 atrioventricular nodal conduction

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sotalol</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>245±30</td>
<td>234±13</td>
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<tr>
<td>1 week</td>
<td>222±15</td>
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<tr>
<td>3 week</td>
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<td>231±20</td>
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<tr>
<td>4 week</td>
<td>205±13</td>
<td>224±13</td>
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††P<0.01 vs Sham group, ¶P<0.01 vs baseline.

**Figure 6.** Histological findings and inter-atrial-conduction time. (A) Interstitial fibrosis in the transverse sections of the right atrial free wall (Masson’s trichrome stain) from a representative Sham dog, Control dog and Sotalol dog. (B) Amount of interstitial fibrosis is compared among three groups. Percent fibrosis in atrial sections in the Control group (black bar, 14.5%) and the Sotalol group (hatched bar, 14.6%) significantly increased when compared with the Sham group (white bar, 1.5%). (C) Time course of inter-atrial conduction time at a basic cycle length (BCL) of 200 ms did not differ between the 2 groups. ††P<0.01 vs Sham group, ¶P<0.01 vs baseline.
Changes in Expression of L-Type Calcium Channel α1c mRNA and Kv4.3 mRNA

Figure 7 displays mRNA expression of L-type Ca\(^{2+}\) channel α1c (A) and Kv4.3 (B). In the Control and Sotalol groups, L-type Ca\(^{2+}\) channel α1c mRNA expression was significantly decreased, compared with the Sham group (Sham, 1.28±0.13; Control, 0.69±0.09; Sotalol, 0.84±0.16, P<0.01 for both groups). Similarly, Kv4.3 mRNA expression showed a tendency to decrease in the Control and Sotalol groups when compared with the Sham group, but the difference among these three groups did not reach statistical significance. d,l–Sotalol treatment did not alter either L-type Ca\(^{2+}\) channel α1c or Kv4.3 mRNA expression, when compared with the Control group.

Discussion

Major Findings

In the present study, we evaluated the long-term electrophysiological effects of d,l–sotalol in a canine AF model induced by ATP with preserved AV conduction. The major findings are as follows. First, d,l–sotalol administration after the development of ATP-induced remodeling reversed abbreviation of AERP and prevented AF perpetuation without aggravation of tachycardia-induced LV dysfunction. Second, d,l–sotalol did not affect ATP-induced changes in L-type Ca\(^{2+}\) channel and Kv4.3 mRNA expression. Third, d,l–sotalol did not affect either ATP-induced increase in the atrial interstitial fibrosis or the enlargement of the LA area.

Previous Studies Regarding the Electrophysiological Effects of d,l–Sotalol on AF

Previous experimental studies have shown that IKr blocking effects of d,l–sotalol have reverse use-dependency and are reduced in the remodeled atria.\(^\text{18-21}\) These electrophysiological characteristics of d,l–sotalol limit its ability to terminate AF. The Canadian Trial of Atrial Fibrillation (CTAF) study and subanalysis from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) demonstrated that d,l–sotalol was less effective in preventing the recurrence of AF than amiodarone.\(^\text{22,23}\) In contrast, the SAFE-T revealed that d,l–sotalol had similar efficacy to amiodarone for pharmacological conversion of persistent AF.\(^\text{8}\) Osaka et al demonstrated that oral administration of d,l–sotalol reversed rate adaptation of monophasic action potential duration and AERP abbreviation in the atria of chronic AF patients.\(^\text{24}\) To our knowledge, the present study is the first experiment to investigate the long-term electrophysiological effects of d,l–sotalol on the atrial remodeling using a canine ATP model.

Potential Mechanisms Underlying the Effects of d,l–Sotalol

In the present study, we demonstrated significant effects of d,l–sotalol on the ATP-induced AF substrate with LV dysfunction, which mimicked AF with tachycardia-induced LV dysfunction. In a canine CHF model induced by ventricular pacing, a decrease in IKs current in the atrium has been reported.\(^\text{25}\) Atrial IKs downregulation in CHF dogs may increase the dependence of repolarization on IKr, so that the IKr blockade produces the greater prolongation of AERP. Therefore, d,l–sotalol could have the greater efficacy on the ATP-induced AF model with LV dysfunction. In addition to its IKr blocking properties, d,l–sotalol has a β-adrenoceptor blocking effect.\(^\text{9}\) The elevation of the sympathetic tone increases IKs currents and this can counteract AERP prolongation by IKr blocker. The combination of the IKr blocking action with the β-adrenoeceptor blocking action may increase the possibility of maintaining class III effect of d,l–sotalol even under the enhanced sympathetic tone.\(^\text{26}\) Although the oral dosage of d,l–sotalol used in the present study was smaller than that used in the clinic, the plasma concentration of sotalol was similar to that showing half-maximal β-blocking effects (0.8±0.3 μg/ml).\(^\text{27}\)

An interesting observation was the delayed prolongation of the shortened AERP after d,l–sotalol administration, despite the plasma concentrations of d,l–sotalol remaining constant. AERP at 2 weeks did not differ from AERP at 1 week. In contrast, QTc at 2 weeks increased significantly when compared with QTc at 1 week (Figure 2). The time course of AERP prolongation induced by d,l–sotalol was gradual, compared with that of QTc. Both AERP and QTc were measured at the same basic cycle length of 400 ms, hence, reverse use-dependent effects of d,l–sotalol could not explain this phenomenon.

In a canine model of AF with ATP, both amiodarone and bepridil prevented L-type Ca\(^{2+}\) channel downregulation and
reversed pacing-induced AERP abbreviation and promotion of AF induction.7,28 In the present study, however, d,l–sotalol could not reverse the downregulation of L-type Ca\(^{2+}\) channel \(\alpha_{1c}\) mRNA expression. Workman et al reported that chronic \(\beta\)-blockade administration decreased the amplitude and density of I\(\text{to}\) in human atrial myocytes, resulting in a prolongation of AERP; however, we could not find any difference in Kv4.3 mRNA expression between the Control and Sotalol groups.10 It is possible that changes in the other channels may contribute to the unique time course of AERP prolongation by d,l–sotalol.

**Influence of d,l–Sotalol on Tachycardia-Induced LV Dysfunction and Atrial Structural Remodeling**

In the present study, rapid ventricular responses during ATP depressed LVEF after 1 week of pacing, and impaired LV function was sustained thereafter. d,l–Sotalol did not alter the degree of reduction in LVEF obtained at 4 weeks. d,l–Sotalol did not affect the atrial structural remodeling such as interstitial fibrosis and the LA enlargement. These findings suggest that the efficacy of d,l–sotalol in preventing AF promotion was not due to the improvement of the LV function or the atrial structural remodeling.

Rapid ventricular responses during ATP could be suppressed by d,l–sotalol administration because of its \(\beta\) blocking action.29 But oral administration of d,l-sotalol at a dose of 2 mg kg\(^{-1}\)·day\(^{-1}\) did not affect ventricular responses probably because tachycardia-induced LV dysfunction enhanced sympathetic tone.

**Study Limitations**

First, AERP was measured only at a single site in the RAA. The refractoriness in the other areas of the atrium and its heterogeneity were not determined. Second, we evaluated the ionic channel expression for the L-type Ca\(^{2+}\) channel \(\alpha_{1c}\) and Kv4.3 only at the mRNA level, but not at the protein or functional level. Third, we did not demonstrate the distinct action of d,l–sotalol between the ATP-induced AF model with controlled ventricular rate and CHF-induced AF model. For these reasons, the mechanisms of reversal of abbreviated AERP by d,l–sotalol remain speculative. Further studies are needed to clarify these points.

**Clinical Implications**

The present study showed that the AERP prolonging effects of d,l–sotalol were well-preserved in the ATP-induced AF model with intact AV conduction, and did not affect depressed LV function. Amiodarone is a gold standard pharmacotherapy for AF patients with LV dysfunction; however, the use of amiodarone is often limited by its extracardiac side-effects.30 From a clinical viewpoint, the present study may provide an experimental basis for use of d,l–sotalol in patients with persistent AF with LV dysfunction.31

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**Disclosure**

Conflict of interest: none declared.


