Antifibrillatory and Proarrhythmic Effects of $d_l$-Sotalol Mediated by the Action Potential Duration Restitution Kinetics

Hui-Nam Pak, M.D., Young-Hoon Kim, M.D., Gyo Seung Hwang, M.D., Soo Jin Lee, M.D., Hyun Soo Lee, M.PH., Hong Euy Lim, M.D. and Young Moo Ro, M.D.
Division of Cardiology, Korea University Cardiovascular Center, Seoul, Korea

ABSTRACT

**Background and Objectives**: The action potential duration (APD) restitution kinetics has been known to play a crucial role in the initiation and maintenance of ventricular tachycardia (VT)/fibrillation (VF). We hypothesized that “the anti-arrhythmic and proarrhythmic effects of $d_l$-sotalol are mediated by changing the APD restitution (APDR) kinetics”. **Materials and Methods**: The purposes of this study were: 1) to assess the effects of $d_l$-sotalol on the APDR kinetics, and 2) to correlate the anti-arrhythmic and proarrhythmic action using the APDR kinetics. We recorded the transmembrane potentials (TMPs), using the microelectrode technique, in seven isolated perfused swine right ventricles, at the baseline, and with 1, 5, 10 and 20 mg/L of $d_l$-sotalol, with a washout period of 1 hour. The ventricular effective refractory periods (VERP), APD at 90% repolarization (APD$_{90}$), spontaneous defibrillation rate and VF inducibility were measured at each concentration. We plotted APDR curves of S1-S2 pacing against VF, and calculated the maximal slopes (Smax) of the APDR. **Results**: Sotalol (10 mg/L) prolonged the APD$_{90}$ (p<0.001) by reducing the Smax of the APDR (by S1-S2 pacing, p<0.01; during VF, p<0.05). Accordingly, 41.7% of the VT/VF was terminated spontaneously, and VT/VF inducibility reduced from 91.1% at the baseline to 25% with 10 mg/L sotalol. A higher dose of sotalol (20 mg/L) increased the Smax, despite continuous prolongation of the VERP and APD$_{90}$, resulting in the increase in the VT/VF inducibility (36.4%). **Conclusion**: Sotalol produces its anti-fibrillatory effect by APD prolongation in parallel with a flattening of the Smax at therapeutic doses. However, a higher concentration of sotalol increased the Smax and VF inducibility in isolated swine ventricular tissue. (Korean Circulation J 2005;35:282–289)

KEY WORDS: Ventricular fibrillation; Sotalol.

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**Introduction**

Ventricular fibrillation (VF) remains the most common cause of sudden death. In clinical settings, VF is almost always preceded by ventricular tachycardia (VT). Although most episodes of induced VT terminate spontaneously, some are maintained, and degenerate to VF. What is the mechanism of such differences? Dispersion of refractoriness is important to maintain reentrant arrhythmias, and is related to the instability of the reentry and wavebreak. Dynamic heterogeneity also plays a crucial role, as the fixed electrophysiological and anatomical heterogeneities in the transition of VT to VF, or wavebreak, are an important mechanism of VF maintenance. The electrical restitution property is one of the major factors influencing this type of the dynamically induced wavebreak. We previously reported the mechanisms of initiation of VF as a wave-wave interaction and a spontaneous wavebreak, with the short wavelength, action potential duration (APD) restitution and APD alternans contributing to the spontaneous wavebreak. The steeper maximal slope (Smax) of the APD restitution (APDR) curve the greater the changes in the myocardium and the more vulnerable it will become to wavebreak and VF. Sotalol is a class III antiarrhythmic drug, and is also known to have proarrhythmic effects. However, detailed electrophysiological mechanisms of these effects remain to be determined. We have hypothesized that the “anti-arrhythmic and proarrhythmic effects of sotalol are mediated by changing the APDR kinetics.”
The purposes of this study were to examine: 1) how sotalol affects the APDR kinetics, and 2) whether these changes affect the vulnerability of the ventricular myocardium with respect to VT/VF.

**Material and Methods**

The study protocol was approved by the Institutional Animal Care and Use Committee, and was consistent with the guidelines of the Korean Society of Circulation.

**Myocardial tissue preparations**

A total of 7 farm swine (body weight of 45.5 ± 3.9 kg) were used. Each animal was anesthetized by intravenous thiopental sodium (20 mg/kg) after an intramuscular injection of ketamine (20 mg/kg). Tracheostomy and endotracheal intubation were performed, and artificial ventilation maintained. The hearts were quickly removed after a midline sternotomy. Details of this model have been reported elsewhere. The right ventricle was separated from the beating heart, the sinus rhythm immediately changed to VF in all the tissues. During sustained VF, we recorded stable TMPs for 5 minutes, and then defibrillated it by gradual increments of the shock energy from 0.5 to 3.0 J (Ventritex HVS-02 defibrillator, biphasic truncated exponential waveform shocks of 6 ms duration). After successful defibrillation, the tissue was paced with a pacing cycle length (PCL) of 600 ms for 5 min (recovery time). Pacing was performed with 2 ms pulse durations at precisely twice the diastolic threshold strength using a programmable electrical stimulator (Bloom and Associate) and constant-current isolation unit (EP Technologies), which allowed fine-tuning of the stimulus output strength within the range <1 mA. The train of eight beats, with 600 ms pacing (S1), was followed by S2 extra-stimulation for the S1-S2 pacing protocol (Fig. 1). The S1-S2 coupling intervals started from 400 ms, were decreased by 20 ms until an S1-S2 coupling interval of 300 ms, and then subsequently decreased by 10 ms until the failure of ventricular capture. The coupling interval was then increased by 8 ms, and finally 2 ms steps down until the ventricular effective refractory period (VERP). After recording the S1-S2 pacing protocol, VF was re-induced by burst pacing (starting at PCL 150 ms, reduction by 10 ms steps until minimal PCL of 1:1 capture, 2 ms pulse duration at 2-fold the threshold current for 5 sec, with a 5 sec interval between each burst pacing, for a maximum number of 20 trials). The VF inducibility was determined by the ratio of the successful VT/VF induction instances to the number of the burst pacing attempts. After TMP recording of the baseline VF and S1-S2 pacing, dl-sotalol (Sigma) was infused during VF, and the same protocol repeated at each concentration (1, 5, 10 and 20 mg/L) and after washout for 1 hour. Monomorphic VT (MVT) was defined when both the bipolar and unipolar electrograms showed regular tachycardia rhythm, whereas rapid irregular ventricular rhythm was classified as VF.

**Data analysis**

The TMP curves were analyzed using custom-designed software (Axoclamp 2A). APD∞ was defined as a 90% repolarization duration and diastolic interval (DI) with the time interval as the previous APD∞ point to the next initiation point of the action potential. At very short S1-S2 intervals, DI was measured as the S1-S2 interval minus the APD of S1. During VF,
the APD and DI were measured using customized software (EDA, Linux), which detected \((dV/dt)_{\text{max}}\) as a reference point of an APD measurement, and calculated the DI and APD. The APDR curve was constructed by plotting the APD of S2 versus the preceding DI. The time course of the restitution was obtained by S1-S2 during VF, and fitted using the monoexponential equation:

\[
y(\text{APD}_{90}) = y_0 + A_1 \left(1 - e^{-\frac{\text{DI}}{\tau_1}}\right)
\]

where \(A_1\) is the free-fitting variable. With each \(A_1\) and \(\tau_1\) for the correspondent DI, the slope was calculated using the equation:

\[
\text{Slope} = \left(\frac{A_1}{\tau_1}\right) \ast \left[\text{Exp}\left(-\frac{\text{DI}}{\tau_1}\right)\right].
\]

In the slope equation, the maximum slope \(\text{Smax}\) was calculated by solving the equation for the value of the shortest diastolic interval (DI), which had been captured at 2-fold the current of the pacing threshold.

**Statistics**

The data are presented as the mean (standard deviation). ANOVA, with Newman-Keuls tests, were used to compare the electrophysiological parameters of each concentration of \(d_1\)-sotalol. Fisher’s exact tests were performed to compare the VT/VF inducibility of each concentration. The null hypothesis was rejected at a value of \(p<0.05\).

**Results**

**Sotalol prolongs APD and VF cycle length**

At an S1 PCL of 600 ms, sotalol prolonged the APD and ERP, in dose-dependent manners (Table 1). The APD at 10 and 20 mg/L sotalol concentrations were both significantly longer than that of the baseline \((p<0.01)\). The morphologies of the action potential curves were not markedly different at different sotalol concentrations (Fig. 1). However, relative shortening of the diastolic interval was observed with short S1-S2 coupling intervals at high concentrations of sotalol (Fig. 1C).

During VF, sotalol also prolonged the APD and VF cycle length (VFCL), in dose-dependent manners (Table 1). Although the mean APD during VF became longer 20 mg/L sotalol than at the baseline, with statistical significance \((p<0.01)\), the VFCL had already become longer with the 5 mg/L sotalol dose \((p<0.05)\). Fig. 2 shows the TMP recordings during VF with a sotalol infusion. Sotalol not only prolonged the APD
Table 1. APD and APDR During S1-S2 Pacing and VF

<table>
<thead>
<tr>
<th></th>
<th>S1-S2 Pacing</th>
<th>VF</th>
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<tbody>
<tr>
<td></td>
<td>Sotalol baseline</td>
<td>Sotalol 1 mg/L</td>
</tr>
<tr>
<td>ERP (ms)</td>
<td>269.0 ± 45.4</td>
<td>253.4 ± 69.9</td>
</tr>
<tr>
<td>APD90 (ms)</td>
<td>108.6 ± 31.3</td>
<td>85.3 ± 18.6</td>
</tr>
<tr>
<td>Smax</td>
<td>3.91 ± 1.62</td>
<td>1.70 ± 1.51</td>
</tr>
<tr>
<td>DI (ms)</td>
<td>25.1 ± 30.5</td>
<td>51.3 ± 43.5</td>
</tr>
<tr>
<td>CL (ms)</td>
<td>143.0 ± 58.2</td>
<td>137.4 ± 46.0</td>
</tr>
<tr>
<td>APD0 (ms)</td>
<td>106 ms</td>
<td>68 ms</td>
</tr>
<tr>
<td>VFCL (ms)</td>
<td>204 ± 10 ms</td>
<td>52 ms</td>
</tr>
</tbody>
</table>

*: p<0.01 vs. baseline, †: p<0.05 vs. baseline, ‡: p<0.001 vs. baseline. APD: action potential duration, ERP: effective refractory period, APD0: action potential duration at 0%, Smax: maximal slope of APDR, DI: diastolic interval, CL: cycle length, APDR: action potential duration restitution, VF: ventricular fibrillation

Fig. 2. TMP recordings of VF and the antifibrillatory effects of sotalol. Sotalol prolonged the VFCL and APD0 during VF. VF became regularized to polymorphic or monomorphic VTs, and was subsequently terminated (D). TMP: transmembrane potential, VF: ventricular fibrillation, VFCL: ventricular fibrillation cycle length, APD0: action potential duration at 90%, Smax: maximal slope of APDR, DI: diastolic interval, CL: cycle length.

and VFCL, but also changed the VF to a more organized form, or VT, and finally its termination. Most of the VF (66.7%) terminated spontaneously during sotalol infusion, which were preceded by oscillation of the VFCL (Fig. 2D).

With 20 mg/L of sotalol, we started to washout the sotalol for 1 hour, and observed the changes of TMP. Although the APD0 returned to the baseline value during S1-S2 pacing (245 ± 6 ms vs. 253 ± 11 ms, p=NS), ERP (411 ± 106 ms vs. 269 ± 45 ms, p<0.05) and VFCL (333 ± 20 ms vs. 143 ± 58 ms, p<0.001), it remained longer than the baseline, suggesting reduced tissue excitability (Table 1).

Sotalol changes the APDR kinetics

During S1-S2 pacing, sotalol reduced the Smax of the APDR curves in a dose dependent manner at therapeutic concentrations (<10 mg/L, p<0.01; Table 1). However, a higher concentration of sotalol (20 mg/L) increased the slope of the Smax of the APDR curves generated by S1-S2 pacing. Fig. 3 shows representative examples of the S1-S2 APDR curves. Because sotalol
resulted in prolongation of the APD 90 and relative shortening of the diastolic interval (DI), the APDR curves shifted to the left upper side with increments in the sotalol concentration. In contrast, the Smax of the APDR curves became flatter at doses of 1 to 10 mg/L compared with the baseline, and that for 20 mg/L sotalol became steeper (Fig. 3).

During VF, sotalol shifted the dynamic APDR curves and changed the Smax dynamic of the APDR in the same manner as the S1-S2 pacing (Table 1). However, the Smax values of the dynamic APDR curves were usually more than 1.0, and higher than that of the S1-S2 pacing. Although sotalol concentrations less than 10 mg/L reduced the Smax of the dynamic APDR curves (p<0.01), a higher concentration of sotalol (20 mg/L) increased the slope of the Smax of the dynamic APDR curve (Fig. 4). Fig. 5A summarizes the patterns of the Smax changes according to the sotalol dose during S1-S2 pacing and VF, which shows a clear dose dependent trend.

**Antiarrhythmic and proarrhythmic effects and sotalol Concentration**

Sotalol terminated the VT/VF (66.7%, Fig. 2D) or converted VF to VT (33.4%) by increasing the APD 90 and reducing the Smax (Table 2). The defibrillation effect of sotalol was noted from a concentration of 1 mg/L, and gradually increased, in a dose-dependent manner (Table 2). The mean concentration resulting in a spontaneous defibrillation was 10.1 mg/L. Most of the induced VF or polymorphic VT was maintained transiently, and converted to VT at concentrations of 5 to 10 mg/L (Table 2). The inducibility of ventricular arrhythmia by burst pacing also reduced with increment of the sotalol concentration at doses between 1 and 10 mg/L (Fig. 5B).

Under the effects of sotalol, most of the arrhythmias induced by burst pacing were VT. However, VF was induced at a high (20 mg/L) concentration of sotalol in the tissue (Fig. 5B). In this particular case, the induced initial rhythm was VT, which quickly degen-
erated to VF, with a steepening of the Smax, despite prolonged ventricular refractoriness and APD90. VT was also induced in other tissue by an S1-S2 single extra-stimulus (S1-600 ms, S2-200 ms) with a sotalol concentration of 20 mg/L (Fig. 1C). The Smax value of the S1-S2 APDR curve was greater than 1.0 (1.90), with a lengthening of the APD90 in that tissue. These findings suggest that an increase in the Smax of the APDR curve, despite APD90 prolongation, is related with the proarrhythmic effect of the high dose of sotalol (Fig. 5).

**Discussion**

Sotalol induces anti-fibrillatory effects through both prolongation of the APD90 and reduction of the Smax. A higher concentration (20 mg/L) of sotalol, however, increased the ventricular tissue vulnerability to VF, by increasing the slope of the Smax, despite the significant prolongation of the APD90.

**APDR as a mechanism of VF initiation and maintenance**

The wavebreak has been known to depends on the preexisting electrophysiological heterogeneity, and particularly on the dispersion of refractoriness. Recently, dynamically induced heterogeneity has been found to be important for the initiation and maintenance of ventricular arrhythmia. One of the major factors influencing this type of dynamically induced wavebreak is the electrical restitution properties, although other factors, such as intracellular calcium cycling, cardiac memory and diffusive currents, also influence the dynamic wave instability. Nolasco and Dahlen have demonstrated that if the restitution curve is sufficiently steep, APD will spontaneously start to oscillate from beat to beat when the tissue is periodically paced at a high frequency. The abnormal conduction velocity restitution is also associated with VF in patients with heart disease. Recently, the tissue discontinuities imposed by structural barriers have been demonstrated to cause abnormal conduction velocity restitution. When this dynamic instability is added to the preexisting electrophysiological heterogeneity, spatial variations of the wavelength amplify the source-sink mismatch with the adjacent waves, causing a localized wavebreak and reentry. Furthermore, by reducing the steepness of the APDR curve, the spiral or scroll wave breakup can be progressively stabilized, and subsequently prevented.

In this study, several electrophysiological characteristics of sotalol have been established. First, sotalol has been established to prolong the APD90, VF cycle length, and to reduce the Smax when given in therapeutic doses. However, the Smax is increased at the proarrhythmia dosage. Second, a direct correlation between the

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**Table 2. VF inducibility and defibrillation rate**

<table>
<thead>
<tr>
<th>Sotalol 0 mg/L</th>
<th>Sotalol 1 mg/L</th>
<th>Sotalol 5 mg/L</th>
<th>Sotalol 10 mg/L</th>
<th>Sotalol 20 mg/L</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT Termination (%)</td>
<td>0</td>
<td>8.3</td>
<td>16.7</td>
<td>16.7</td>
<td>25.0</td>
</tr>
<tr>
<td>VF to VT (%)</td>
<td>0</td>
<td>0</td>
<td>16.7</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>VT Inducibility (%)</td>
<td>66.7</td>
<td>50.6</td>
<td>40.0</td>
<td>25.0</td>
<td>27.9</td>
</tr>
<tr>
<td>VF Inducibility (%)</td>
<td>24.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9.1</td>
</tr>
</tbody>
</table>

VF: ventricular fibrillation, VT: ventricular tachycardia
VT/VF inducibility and APDR slope has been demonstrated. The proarrhythmic effect of sotalol at a high dose may have triggered activity. However, it is difficult to differentiate triggered activity and micro re-entry at the tissue level, with the restitution property having important roles in the maintenance of VF, regardless of the initiation mechanism. Therefore, reduction of the dynamic instability, by flattening the APDR slope, may turn out to be a promising target for the prevention of VF.

Wu et al.\textsuperscript{18} recently reported a slow and relatively organized type II VF, which was noted with a flat APDR, low tissue excitability and steep conduction velocity restitution curve. According to their hypothesis, “VF inducibility is not always determined by the absolute number of Smax greater than 1, because a slow type II VF could be induced, even with a flat APDR curve in the tissue with low excitability.”\textsuperscript{18,19} Laurita et al.\textsuperscript{20} showed that APD alternans can be spatially discordant, where one region is in the short APD phase, while the rest of the region exhibits the long APD phase of the alternans, causing greater dispersion of repolarization and conduction block of the following beats. Several groups have demonstrated that discordant alternans may be formed, even with uniform APDR, which is most likely due to a non-uniform conduction delay.\textsuperscript{21-24} Cardiac structures have also been implicated in wavebreak and reentry by influencing the wavefront dynamics of VF.\textsuperscript{24-27} The geometry of the ventricular wall, in particular the wall thickness, is also an important determinant of VF maintenance.\textsuperscript{26,27}

**Anti-fibrillatory effects of sotalol**

The most commonly used classification of antiarrhythmic agents is the Vaughan-Williams classification,\textsuperscript{28,29} which classifies the antiarrhythmic drugs according to their effects on the regulation of the ion channels of the myocardial cell membrane. The effects of each drug on the dynamic electrophysiological properties of the myocardial cells are not fully understood. Recently, bretylium,\textsuperscript{8} amiodarone\textsuperscript{30} and procainamide\textsuperscript{12} have been demonstrated to produce a flattening effect on the APDR. This study has demonstrated that sotalol can induce antifibrillatory effects, mainly through its anti-restitution property. However, a high dose of sotalol has been shown to increase the dynamic instability by increasing the slope of the APDR, even with a lengthening of the APD\textsubscript{50}, and this condition demonstrated a proarrhythmia.

The one-hour washout period data showed longer VFCL and ERP than at the baseline, in contrast to the observation that the APD\textsubscript{50} returned to the baseline value (Table 1). All induced arrhythmia during the washout period was monomorphic VT, not VF (Fig. 5B). This finding suggests that a 1-hour washout period is not sufficient to eliminate the d\textsubscript{l}-sotalol accumulated in the cardiac tissue, and sotalol also affects the tissue excitability, which may contribute to the antiarrhythmic action. The beta-adrenoceptor blocking action of sotalol may account, in part, for the antiarrhythmic action and ERP prolongation, as beta-adrenoceptor blocker prevents the mecanoelectrical feedback related to APD shortening.\textsuperscript{30}

**Clinical implications**

Cardiac Arrhythmia Suppression Trial (CAST)\textsuperscript{31} or Survival with Oral Sotalol (SWORD)\textsuperscript{32} studies show that a significant decrease of ventricular premature beats fails to prevent sudden cardiac death. In other words, suppression of VF initiators cannot always prevent VF maintenance. Rather a high dose of the anti-arrhythmic drug results in proarrhythmia. The main mechanism of VF maintenance is the wavebreak, which is closely related to the APDR kinetics. Therefore, it is necessary that anti-arrhythmic agents should reduce the Smax of the APDR and the tissue excitability to suppress the VF maintenance, not just to suppress its initiation.\textsuperscript{40,41} Drugs or techniques of intervention, with anti-fibrillatory effects, might be further tested to see whether they have effective anti-restitution properties and can prevent the risk of sudden cardiac death.

**Limitations**

We did not evaluate the effects of sotalol on the conduction velocity and tissue excitability in the light of its mechanism of antiarrhythmic action. Although APDR measured using the dynamic (rapid-pacing) restitution protocol may be superior to the S1S2 method in predicting the propensity for VT and APD alternans,\textsuperscript{23} dynamic APDR curve during VF might substitute the pacing induced dynamic APDR curves in this study. Whether the results of the present study, obtained through TMP recordings at a single cell of the isolated ventricular tissue, are applicable to humans remain to be tested.

**Conclusion**

Sotalol can produce antiarrhythmic and proarrhythmic effects through changes in the APDR kinetics. The slope of the APDR is one of the key determinants of the ventricular tissue vulnerability to VF. Drugs or techniques of intervention, with anti-fibrillatory effects, might be further tested to see whether they have effective anti-restitution properties and thus, can prevent the risk of sudden cardiac death.

**Acknowledgments**

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