Electrophysiologic Actions of dl-Sotalol in Patients With Persistent Atrial Fibrillation

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OBJECTIVES

We sought to determine the electrophysiologic actions of sotalol in the remodeled atrium of humans.

BACKGROUND

In experimental studies, sotalol has limited class III action in the electrically remodeled atrium and did not prevent atrial fibrillation (AF) induction.

METHODS

We determined the effective refractory periods (ERPs) at three pacing cycle lengths (400, 500, and 600 ms) in the high right atrium (HRA) and distal coronary sinus (DCS) before and after intravenous infusion of dl-sotalol in 10 patients with persistent AF who underwent internal cardioversion. The same protocols were performed in 10 control subjects in sinus rhythm.

RESULTS

In the HRA and DCS, the atrial ERPs at different drive cycle lengths were significantly shorter in patients with AF than in control subjects (p < 0.05). In patients with AF, the atrial ERP’s adaptation to rate was nearly normal in the HRA, but was poor in the DCS. In both groups, dl-sotalol significantly increased the atrial ERPs at both the HRA and DCS, as compared with baseline (p < 0.05). However, the prolongation of atrial ERPs was significantly less at a drive cycle length of 600 ms in patients with AF versus control subjects (p < 0.05). After infusion of dl-sotalol, the atrial ERP’s adaptation to rate at both the HRA and DCS was poor in patients with AF, and AF was still easily inducible in the majority of them, but not in control subjects.

CONCLUSIONS

The results of the present study demonstrate that the electrophysiologic actions of dl-sotalol are significantly attenuated in the chronically remodeled human atrium, and these changes might represent a probable explanation for the low efficacy of dl-sotalol to prevent early AF recurrence after electrical cardioversion.

Experimental and clinical studies have shown that atrial fibrillation (AF) resulted in electrical remodeling of the atrium and increased the susceptibility to further episodes of AF (1–4). Although these electrophysiologic changes appeared to be reversible after restoration and maintenance of sinus rhythm (5,6), they might affect the efficacy of anti-arrhythmic agents in preventing early AF recurrence. Despite the use of anti-arrhythmic therapy, AF frequently recurs within the first two weeks after electrical cardioversion (7,8).

Sotalol is a class III anti-arrhythmic agent commonly used in patients with AF. It prolongs the atrial action potential duration by blocking the delayed rectifier potassium channel (IKr) (9), but its effect declines at a rapid rate with reverse-use dependency (10,11). Recent animal studies revealed that sotalol exerted a limited class III effect during AF in the remodeled atrium and failed to prolong the atrial refractory period after cardioversion of persistent AF (12,13). Although the mechanism remains unclear, these studies suggested that AF-induced atrial electrical remodeling might affect the electrophysiologic actions of anti-arrhythmic agents on the atrium. No previous studies have examined the effects of sotalol in the remodeled atrial myocardium of humans. Therefore, the aim of the present study was to assess the effect of sotalol on atrial refractoriness in humans after electrical cardioversion of persistent AF.

METHODS

Patients. The study included 10 patients with persistent AF (duration between three months and three years) admitted for internal cardioversion. The diagnosis of AF was based on the surface electrocardiogram (ECG), which showed a fluctuation from baseline without regular P or F waves and with totally irregular RR intervals. All patients were evaluated by taking a detailed clinical history and physical examination, as well as relevant laboratory investigations such as a thyroid function test and transthoracic echocardiography. They were anticoagulated with warfarin to achieve an International Normalized Ratio (INR) of 2 to 3 for at least four weeks. All anti-arrhythmic drugs were discontinued for at least five half-lives. No patients received amiodarone within six months before the study. Patients with the following conditions were excluded from the study: 1) AF due to reversible causes; 2) unstable angina or myocardial infarction within six months; 3) class III or IV heart failure; 4) history of thromboembolism within six months; 5) corrected QT interval >450 ms; 6) contraindications or previous intolerance to sotalol; and 7) inability to complete the study protocol because of either failure in cardioversion or frequent, sustained AF (>3 episodes) induced or occurring spontaneously during electrophysiologic study, requiring repeat cardioversion.
Ten age-matched patients with supraventricular tachycardia (three with atrioventricular node reentry tachycardia and seven with atrioventricular reciprocating tachycardia) were included as the control group. These patients had no structural heart disease and no clinical atrial flutter or fibrillation.

**Electrophysiologic study.** All patients underwent instrumentation with two custom-built 6F decapolar catheters (Elacath Inc., Rahway, New Jersey) for internal cardioversion and/or electrophysiologic study. Each catheter has five pairs of stainless-steel rings with 2-mm interelectrode spacing within each pair and 5-mm spacing between each pair. One catheter was positioned along the high (anterolateral) right atrium (HRA), and the other was advanced into the distal coronary sinus (DCS). An additional quadripolar electrode catheter was placed in the right ventricular apex for shock synchronization. Surface ECG leads II and V1 and intracardiac electrograms from HRA and DCS were displayed on an oscilloscope and recorded at a paper speed of 100 mm/s (PPG, MIDAS 5000, Lenexa, Kansas). Pacing was performed with a programmable stimulator (EP3, EPMedSystem, New Jersey).

**Study protocol.** The study was approved by our Institutional Ethical Committee, and all the patients gave written, informed consent. In all patients with persistent AF, internal cardioversion was performed by using an external atrial defibrillator (XAD, InControl, Inc., Redmond, Washington) capable of delivering R-wave–synchronized biphasic shocks (3-ms/3-ms waveform) of up to 6 J, as described previously (14). After restoration of sinus rhythm, a 15-min waiting period was observed to allow short-term, rate-related changes in the atrial effective refractory period (ERP) to dissipate (15). In the control group, the study protocol was performed after completion of the radiofrequency ablation procedure.

A pair of bipolar electrodes from each of the HRA and DCS catheters was selected for programmed stimulation, so that the pacing threshold was <1.0 mA (mean atrial pacing threshold of 0.8 ± 0.1 mA). Pacing was performed at twice the diastolic stimulation threshold using a 2-ms pulse duration. The atrial pacing threshold at each site was then verified at the end of the stimulation protocol. When a significant difference in the pacing threshold was found (>0.5 mA), the data were not considered for analysis; either another pair of electrodes was selected or the catheter was repositioned, and the stimulation protocol repeated. At the HRA and DCS, the atrial ERP was measured at basic cycle lengths of 400, 500, and 600 ms, with drive train of 8 beats and a 3-s pause between pacing trains, in random order. The initial S1–S2 interval was set to be shorter than the atrial ERP, and the S1–S2 interval was increased in steps of 5 ms until there was atrial capture. The atrial ERP was defined as the longest S1–S2 interval that failed to result in atrial capture. The atrial ERP were measured twice at each drive cycle length and averaged. Patients who developed sustained AF (>10 min) during the determination of atrial ERPs were internally cardioverted. Patients with more than three episodes of sustained, secondarily induced AF were excluded from the analysis. Because short episodes of AF can affect atrial refractoriness for several minutes (16), the study protocol was suspended for 15 min after spontaneous or electrical cardioversion.

After the baseline atrial ERP measurement, an intravenous infusion of dl-sotalol (1.5 mg/kg body weight for the loading dose over 10 min and 0.2 mg/kg per h for maintenance) was administrated to all patients. Ten minutes after the loading dose was given, the atrial ERP was measured, as in the baseline study.

**Statistical analysis.** Continuous data are presented as the mean value ± SD. Nonparametric data were analyzed by the chi-square test with Yates’ correction or by the Fisher exact test. The atrial ERP measurements at baseline and after sotalol infusion at different basic cycle lengths were analyzed by analysis of variance with repeated measures. In the HRA and DCS, the linear correlation between the ERPs and corresponding pacing cycle lengths was calculated by single linear regression. The presence of normal or abnormal ERP’s adaptation to rate and its degree were also determined by measurement of the slope values, as described previously (5). When a negative or positive slope value was between 0.01 and 0.04, the adaptation were poor; between 0.05 and 0.06, it was considered as nearly normal; and ≥0.7, it was classified as normal. The paired Student t test was used to compare the change in ERP after antiarrhythmic drug administration. A value of p < 0.05 was considered as statistically significant.

**RESULTS**

**Patients.** There were eight men and two women with AF (mean ±SD age 59 ± 12 years). Their mean AF duration was 198 ± 360 days (range 90 to 1,440). Their mean left ventricular ejection fraction was 0.61 ± 0.11, and their left atrial diameter was 40.6 ± 6.3 mm (range 38 to 54). Underlying heart disease was present in six patients: hypertension (n = 4), valvular heart disease (n = 1), and dilated cardiomyopathy (n = 1). Four patients had only AF. In the control subjects, there were seven men and three women (mean age 57 ± 10 years). Their mean left ventricular ejection fraction was 0.67 ± 0.09, and their left atrial diameter was 32.5 ± 4.2 mm. Patients with AF had a significantly larger left atrial size (p < 0.01) and a lower left ventricular ejection fraction (p < 0.05) as compared with control subjects.

**Abbreviations and Acronyms**

AF = atrial fibrillation  
DCS = distal coronary sinus  
ERP = effective refractory period  
HRA = high right atrium  
I_{Kr} = delayed rectifier potassium channel
The ERP's adaptation to rate. The mean atrial ERPs measured in the HRA and DCS in both patients with AF and control subjects are reported in Table 1. The atrial ERPs at drive cycle lengths of 400, 500, and 600 ms in the HRA and DCS were significantly shorter in patients with AF than in control subjects.

As shown in Figure 1, there was a linear correlation between the mean atrial ERPs and the drive cycle lengths in the HRA \((r = 0.94, \text{mean slope value 0.06} \pm 0.03)\), but not in the DCS \((r = 0.46, \text{mean slope value 0.02} \pm 0.05)\) in patients with AF. In the control subjects, there was a linear correlation between the mean atrial ERPs and the drive cycle lengths in the HRA \((r = 0.96, \text{mean slope value 0.08} \pm 0.02)\) and in the DCS \((r = 0.93, \text{mean slope value 0.09} \pm 0.04)\). Therefore, a nearly normal adaptation of the atrial ERPs to the rate was present in the HRA but not in the DCS in patients with AF.

**Effects of dl-sotalol on ERPs.** In both patients with AF and control subjects, dl-sotalol significantly increased the mean atrial ERPs measured in both the HRA and DCS at different drive cycle lengths, as compared with baseline (all \(p < 0.05\) vs. baseline) (Table 1). The mean prolongation of atrial ERPs at the HRA and DCS in both patients with AF and control subjects after infusion of dl-sotalol is shown in Figure 2. In patients with AF, there were no significant differences in the prolongation of atrial ERPs in the HRA and DCS with an increasing drive cycle length \((p > 0.05)\). In control subjects, the prolongation of atrial ERPs in the HRA and DCS after infusion of dl-sotalol increased with lengthening of the drive cycle length from 400 to 600 ms \((p < 0.05)\). As a result, the prolongation of atrial ERPs in the HRA and DCS at a drive cycle length of 600 ms was significant longer in control subjects than in patients with AF \((p < 0.05)\). Therefore, a reverse rate-dependent prolongation of atrial ERPs, as observed in control subjects after infusion of dl-sotalol, was absent in patients with AF.

As shown in Figure 1, adaptations of atrial ERPs to the rate in the HRA \((r = 0.34, \text{mean slope value 0.03} \pm 0.06)\) and in the DCS \((r = 0.56, \text{mean slope value 0.03} \pm 0.05)\) were poor in patients with AF after infusion of dl-sotalol. Adaptations of atrial ERPs to the rate in the HRA \((r = 0.93, \text{mean slope value 0.09} \pm 0.04)\) and in the DCS \((r = 0.95, \text{mean slope value 0.09} \pm 0.04)\) remained normal in control subjects after infusion of dl-sotalol.

**Induction of secondary AF episodes.** At baseline, a secondary episode of AF was induced during 60 (38%) of 160 measurements of atrial ERP in 9 (90%) patients with AF. In control subjects, secondary AF was induced during 22 (15%) of 144 measurements of atrial ERPs \((p < 0.01\) vs. patients with AF) in 4 (40%) patients \((p = 0.06\) vs. patients with AF).

### Table 1. Atrial Effective Refractory Periods at Baseline and After dl-Sotalol Infusion

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<tr>
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<th>Baseline</th>
<th>After dl-Sotalol</th>
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<tr>
<td></td>
<td>Basic Cycle Length</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 ms</td>
<td>500 ms</td>
</tr>
<tr>
<td>HRA</td>
<td></td>
<td></td>
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<tr>
<td>Patients with AF</td>
<td>173 ± 28</td>
<td>181 ± 24</td>
</tr>
<tr>
<td>Control subjects</td>
<td>188 ± 14*</td>
<td>195 ± 16*</td>
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<tr>
<td>DCS</td>
<td></td>
<td></td>
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<tr>
<td>Patients with AF</td>
<td>183 ± 22</td>
<td>185 ± 24</td>
</tr>
<tr>
<td>Control subjects</td>
<td>201 ± 15†</td>
<td>213 ± 18†</td>
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</tbody>
</table>

*p < 0.05 versus patients with AF. †p < 0.01 versus patients with AF. Data are presented as the mean value ± SD.

AF = atrial fibrillation; DCS = distal coronary sinus; HRA = high right atrium.

![Figure 1. Relationship between the pacing cycle length and atrial effective refractory periods (ERPs) measured in the high right atrium (HRA) (A) and distal coronary sinus (DCS) (B) in patients with atrial fibrillation (AF) and control subjects before and after intravenous infusion of dl-sotalol. Solid squares = control subjects at baseline; solid triangles = patients with AF at baseline; open squares = control subjects after dl-sotalol infusion; open triangles = patients with AF after dl-sotalol infusion.](image-url)
Electrophysiologic Actions of Sotalol

DISCUSSION

Main findings. The results of the present study demonstrate that the electrophysiologic actions of dl-sotalol were significantly reduced in the chronically remodeled human atrium. Compared with the control subjects, infusion of dl-sotalol in patients with AF resulted in a lesser prolongation of atrial ERPs at a long drive cycle length and loss of the reverse-use-dependent property and failed to prevent induction of secondary AF.

Changes in dl-sotalol action in the remodeled atrium. Although dl-sotalol has been shown to be effective in preventing early re-initiation of AF after cardioversion by suppression of atrial premature beats (14), AF still recurs in a significant proportion of patients within the first two weeks (17). The relative lack of efficacy of dl-sotalol in preventing early AF recurrence remains obscure. dl-Sotalol has both class II and III anti-arrhythmic effects by its anti-adrenergic effect and blockage of the I_Kr channel, respectively (9). Previous experimental studies have demonstrated that sotalol showed a dose-dependent prolongation of atrial ERPs and prevented AF initiation; however, its effect on atrial ERPs declined at a rapid rate with reverse-use dependency (10,11). It has been postulated that the reverse-use-dependent properties of class III agents were due to the use-dependent accumulation of potassium current, which counteracts the use-dependent blockage of the potassium channel (18). Although the use-dependent property of sotalol might limit the efficacy of sotalol in terminating AF, Derakhchan et al. (19) showed that sotalol prevented AF initiation by atrial premature beats by increasing the atrial ERP at a slower resting sinus rate. Thus, the use-dependent property might contribute to electrophysiologic mechanism of sotalol for the prevention of AF. Recently, Wijffels et al. (12,13) demonstrated that sotalol exerted a limited class III effect and failed to prolong atrial ERPs both during AF and after cardioversion in a goat model of persistent AF. These findings suggest that the electrophysiologic actions of sotalol might be attenuated in the remodeled atrium. Moreover, in addition to reduced ERP prolongation by sotalol in the remodeled atrium, changes in mechanisms underlying AF vulnerability with remodeling, including increased ERP heterogeneity, could have contributed to the reduced clinical efficacy of sotalol (20). Previous experimental studies have demonstrated that sotalol does not decrease atrial refractory heterogeneity during AF (21).

This study confirmed that the changes in the electrophysiologic properties of the remodeled atrium in humans resulted in shortening and loss of rate adaptation of the atrial ERP, with more pronounced changes in the DCS than in the HRA (2,3,6). To our knowledge, this is the first study to investigate the electrophysiologic actions of dl-sotalol in the remodeled human atrium. In this study, patients with long-standing AF were studied to determine the effect of AF-related atrial remodeling on the electrophysiologic action of dl-sotalol. Although dl-sotalol also prolonged the atrial ERP at the HRA and DCS in patients with AF, prolongation of atrial ERPs at a slower rate was significantly less than that in control subjects. As a result,
the reverse-rate dependency of sotalol was lost in patients with AF. Furthermore, sotalol further impaired the rate adaptation of atrial refractoriness in patients with AF. These changes in the electrophysiologic actions of dl-sotalol in the remodeled atrium might account for its limited efficacy to prevent induction of secondary AF in the majority of patients with AF.

Previous experimental studies have demonstrated that AF-related atrial remodeling affects the anti-arrhythmic drug actions. Li et al. (22) have reported a marked differences in the effects of the class III agent dofetilide in different animal models of sustained AF. Sato et al. (23) have also demonstrated that tachycardia-induced remodeling significantly attenuated the prolongation of atrial refractoriness by the class IC agent pilscainide. The exact mechanism for the changes in the electrophysiologic action of dl-sotalol in the remodeled atrium remains unclear. There are several potential mechanisms in which AF-related ionic remodeling could alter the electrophysiologic actions of dl-sotalol (24). If the ionic current or channel against which a drug is targeted is reduced by remodeling, the drug would be expected to have a limited effect on the action potential. Recent studies have demonstrated that the amount of messenger ribonucleic acid and/or protein expression of HERG decreased in goats (25) and patients with persistent AF (26,27). This ionic remodeling may reduce the sensitivity of the atrial myocytes to dl-sotalol. Furthermore, the changes in the action potential profile caused by atrial remodeling can reduce the response to sotalol. It has been postulated that only a small amount of I_Ks is activated during the short plateau of the AF-related remodeled action potential (28). As a result, prolongation of atrial refractoriness produced by I_Ks blockage with sotalol would be reduced. Whether reversal or prevention of the AF-induced electrical remodeling and ionic remodeling after restoration and maintenance of sinus rhythm (5,6), or by using other agents, such as calcium channel blockers (29,30), restores the electrophysiologic actions of dl-sotalol in the atrium and improves its efficacy in preventing AF requires further study.

**Study limitations.** This study has several limitations. First, the ERP was measured only at one site in the HRA and one site in the DCS; therefore, the effects of sotalol on refractoriness in other areas of the atrium or on the heterogeneity of refractoriness remain unknown. Second, patients with a diseased atrium but without AF were not included in this study. Whether the observed effects of sotalol in patients with AF are related to the presence of AF or the diseased atrium is unclear. Third, the monophasic action potential was not recorded in this study, and the action potential duration could not be measured. The use of monophasic action potential recordings, together with ERP measurements, might provide a better insight into the true mechanism of the effects of sotalol in the remodeled atrium. Finally, only the short-term effect of sotalol immediately after cardioversion was investigated in this study. The long-term effect of sotalol in the remodeled atrium remains unknown.

**Conclusions.** The electrophysiologic actions of dl-sotalol change significantly in the remodeled atrium of humans and limit its efficacy in preventing AF recurrence early after cardioversion. Recent clinical studies have suggested that pretreatment with calcium channel blockers, such as verapamil, to attenuate AF-induced remodeling before cardioversion may provide a synergistic effect with other anti-arrhythmic agents, thus preventing AF recurrence (7,31). Therefore, future anti-arrhythmic therapy for AF may need to target not only the atrial electrophysiologic properties, per se, but also the changes in atrial electrophysiology resulting from AF-induced remodeling.

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