Sympathetic Activation, Ventricular Repolarization and I_{kr} Blockade: Implications for the Antifibrillatory Efficacy of Potassium Channel Blocking Agents

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Objectives. The aim of the present study was to test, in vivo and in vitro, the influence of adrenergic activation on action potential prolongation induced by the potassium channel blocking agent d-sotalol.

Background. d-Sotalol is not effective against myocardial ischemia–dependent ventricular fibrillation in the presence of elevated sympathetic activity. Most potassium channel blockers, such as d-sotalol, affect only one of the two components of I_k (I_{kr}) but not the other (I_{ks}). I_{ks} is activated by isoproterenol. An unopposed activation of I_{ks} might account for the loss of anti-fibrillatory effect by d-sotalol in conditions of high sympathetic activity.

Methods. In nine anesthetized dogs we tested at constant heart rate (160 to 220 beats/min) the influences of left stellate ganglion stimulation on the monophasic action potential prolongation induced by d-sotalol. In two groups of isolated guinea pig ventricular myocytes we tested the effect of isoproterenol (10^{-9} mol/liter) on the action potential duration at five pacing rates (from 0.5 to

2.5 Hz) in the absence (n = 6) and in the presence (n = 8) of d-sotalol.

Results. In control conditions, both in vivo and in vitro, adrenergic stimulation did not significantly change action potential duration. d-Sotalol prolonged both monophasic action potential duration in dogs and action potential duration of guinea pig ventricular myocytes by 19% to 24%. Adrenergic activation, either left stellate ganglion stimulation in vivo or isoproterenol in vitro, reduced by 40% to 60% the prolongation of action potential duration produced by d-sotalol.

Conclusions. Sympathetic activation counteracts the effects of potassium channel blockers on the duration of repolarization and may impair their primary antifibrillatory mechanism. An intriguing clinical implication is that potassium channel blockers may not offer effective protection from malignant ischemic arrhythmias that occur in a setting of elevated sympathetic activity.

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The results of the Cardiac Arrhythmia Suppression Trial (1) and of subsequent trials (2,3) were interpreted by many as a message to shift from sodium to potassium channel blocking agents the hope for effective pharmacologic prevention of sudden cardiac death in patients with ischemic heart disease. This interpretation was largely due to the traditional assumption that the apparent efficacy of amiodarone (4,5) depends primarily on its effect of prolonging action potential duration and, hence, ventricular refractoriness. However, amiodarone is much more than a selective potassium channel blocker as it is

also a sodium and calcium channel blocker, an antiadrenergic agent and a coronary vasodilator (6).

The available experimental data on the efficacy of potassium channel blockade in preventing ischemia-induced ventricular fibrillation are not uniform. d-Sotalol (7) did not protect conscious dogs with a healed myocardial infarction from ventricular fibrillation triggered by the combination of transient myocardial ischemia and elevated sympathetic activity due to physical exercise and autonomic reflexes (8). In the same animals adequate protection was provided by the racemic compound d,l-sotalol, which also possesses beta-adrenergic blocking activity (7). By contrast, d-sotalol showed a powerful antifibrillatory effect in postinfarction conscious dogs studied in another experimental preparation in which sympathetic activity is not a critical element in the genesis of lethal arrhythmias (9).

The hypothesis tested in the present study is that sympathetic excitation may interfere with the mechanisms of action of some antiarrhythmic drugs, and specifically with potassium channel blockers. This concept has far-reaching theoretic and clinical implications and warrants adequate investigation. The

basis for this hypothesis stems from the evidence that the potassium current with the largest effect on ventricular repolarization, the delayed rectifier, I_k, comprises two components: one rapidly activated (I_{kr}) and one slowly activated (I_{ks}) (10). I_{kr} is blocked by most of the currently available potassium channel blockers, such as d-sotalol, whereas I_{ks} is not blocked by d-sotalol and is activated by isoproterenol. In conditions of elevated sympathetic activity I_{ks} becomes the predominant component of I_k (11). Thus, in the presence of enhanced sympathetic activity the sheer blockade of I_{kr} may have a limited effect on action potential duration. To explore this concept, we performed two series of experiments in vivo and in vitro. The effect of potassium channel blockade was tested before and after sympathetic stimulation on ventricular monophasic action potentials in dogs, and on transmembrane action potentials of guinea pig isolated ventricular myocytes. Preliminary data have been presented (12,13).

Methods

In Vivo Study

Surgical preparation. Nine healthy adult mongrel dogs (15 to 20 kg) were anesthetized by thiopental sodium (20 mg/kg body weight) followed by alpha-chloralose (80 mg/kg plus 10 to 15 mg/kg as needed). Through a left thoracotomy in the fourth intercostal space, the left stellate ganglion was isolated from the surrounding tissue and prepared for electrical stimulation. The pericardium was opened and the heart suspended in a cradle. In three dogs the sinus node was crushed to prevent the spontaneous sinus rate from exceeding, during adrenergic stimulation, the paced rate at 160 beats/min. A catheter for monophasic action potential recording was positioned on the endocardium of the posterior wall of the left ventricle. This site was chosen because it is the area primarily innervated by the left-sided cardiac sympathetic nerves. Plunge electrodes were placed in the right atrium to pace the heart. Throughout the experiments, arterial blood pressure, the surface electrocardiogram (ECG) and heart rate were recorded. Body temperature was maintained in the normal range by means of a heating pad. The signals were processed by custom-made direct-current amplifiers, digitized at a sampling rate of 1,000 Hz and fed in a Bard Electrophysiology computer system. Ventricular monophasic action potentials were recorded by means of bipolar pressure contact silver-silver chloride custom-built electrodes according to the technique described by Franz et al. (14). Signals were considered acceptable if their amplitude exceeded 15 mV. The monophasic action potential duration was calculated at 90% of repolarization. Each value reported represents the average of three measures for each experimental condition.

In Vitro Study

Isolated guinea pig ventricular myocytes were obtained by enzymatic digestion with the use of a modification of a previously described method (15). Transmembrane action potentials were recorded by means of standard glass intracellular microelectrodes connected to a high impedance amplifier (Axoclamp A2, Axon Instrument). Cells were stimulated with 0.7- to 2.5-mV square wave impulses lasting 3 to 5 ms. Action potential duration (APD) was measured at 80% (APD80) of repolarization. The duration and amplitude of the action potential and resting membrane potential were measured without knowledge of other data.

Experimental Protocols

In vivo. Monophasic action potentials were recorded at 160, 180, 200 and 220 beats/min. To obtain steady state measurements, the baseline pacing rate was maintained for at least 2 min. The left stellate ganglion was then stimulated (10 to 15 V, 10 to 15 Hz, 3-ms pulse duration) for 20 to 30 s. Data were collected throughout the trial up to 30 s after the end of the stimulation, which was considered satisfactory if it produced a systolic blood pressure increase of ≥20 mm Hg. Ten minutes was allowed for recovery between each stimulation. The same protocol performed in control conditions was repeated after intravenous bolus administration of 8 mg/kg of d-sotalol and again after intravenous injection of propranolol, 0.5 mg/kg. In three dogs data could not be collected at 180 beats/min because the spontaneous heart rate during left stellate ganglion stimulation exceeded the paced rate. Data with d-sotalol and propranolol were not collected at 220 beats/min because of the occurrence of atrioventricular block. The effect of propranolol was studied in seven dogs at 180 beats/min and six dogs at 200 beats/min.

In vitro. Cells were placed in the experimental chamber mounted on an inverted microscope (Nikon TMS Inverted Microscope) and continuously perfused with 1.2 mmol/liter calcium HEPES buffered solution. Temperature and pH were kept within the physiologic range throughout the study protocol (pH 7.35, 37.5°C). Only rod-shaped myocytes, noncontracting, with clear striations and with physiologic resting membrane potential were studied. After cell impalement, an equilibration period of approximately 15 min was allowed, then stimulation threshold was assessed and stimulation intensity adjusted. Cells were paced at frequencies of 0.5, 1, 1.5, 2 and 2.5 Hz for ≥50 beats. The protocol was repeated 15 min after the addition of isoproterenol, 10^{-9} mol/liter (n = 6), or d-sotalol, 10^{-5} mol/liter (n = 8), to the perfusion solution. The 10^{-9}-mol/liter isoproterenol concentration was chosen because it mimics the norepinephrine level in myocardial interstitial fluid (16). In the d-sotalol group the pacing protocol was performed a third time after 20 min of combined exposure to d-sotalol and isoproterenol, 10^{-9} mol/liter.

Statistical analysis. Data are presented as mean value ± 1 SD. Differences were tested by one-way analysis of variance for repeated measures (ANOVA) and Scheffé F test (SPSS for Windows, SPSS Inc.). Values of $p < 0.05$ were considered statistically significant.

Table 1. Effect of Left Stellate Ganglion Stimulation and d-Sotalol on Monophasic Action Potential Duration In Vivo

Pacing Rate (beats/min)	Monophasic Action Potential Duration (ms)				ΔAPD90 (%)	
	Control	LSGstim	d-Sotalol	d-Sotalol + LSGstim	After d-Sotalol	After d-Sotalol + LSGstim
160 (n = 3)	216 ± 28	191 ± 31	268 ± 41	234 ± 39	24%	8.3%
180 (n = 6)	190 ± 35	175 ± 31	227 ± 42*†	205 ± 34†‡	19.5%	7.9%
200 (n = 9)	165 ± 31	152 ± 21	197 ± 32*†	179 ± 35†‡	19.4%	8.5%
220 (n = 7)	158 ± 25	152 ± 22	188 ± 28*†	176 ± 27*†‡	19%	11.4%

*p < 0.01 versus control. †p < 0.01 versus left stellate ganglion stimulation (LSGstim). ‡p < 0.01 versus d-sotalol. Values are expressed as mean value ± SD. Statistical analysis of the data obtained at a pacing rate of 160 beats/min was not performed because of the small sample size. ΔAPD90 = change in action potential duration at 90% of repolarization.

Results

In vivo. Nine dogs were studied at a pacing rate of 200 beats/min, seven at 220, six at 180 and three at 160 beats/min. The results are summarized in Table 1. Sympathetic stimulation slightly reduced monophasic action potential duration by 4% to 8% (p = NS).

d-Sotalol increased (p < 0.01) monophasic action potential duration at all rates (from 24% at 160 beats/min to 19% at 220 beats/min). After d-sotalol, the shortening effect of left stellate ganglion stimulation on monophasic action potential duration became significant (p < 0.01).

Most of the prolonging effect of d-sotalol on action potential duration was lost with left stellate ganglion stimulation. Adrenergic activation caused a loss of 65% of the prolongation of monophasic action potential duration induced by d-sotalol at 160 beats/min, of 62% at 180 beats/min, of 56% at 200 beats/min and of 39% at 220 beats/min.

Propranolol abolished the effects of sympathetic stimulation. Monophasic action potential durations at 180 and 200 beats/min were, respectively, 221 ± 31 and 202 ± 26 ms before left stellate ganglion stimulation and remained 219 ± 32 and 199 ± 24 ms after stimulation.

In vitro. Isoproterenol, at the dose used in the present study (10^{-9} mol/liter), produced minimal or no change in APD80 at all pacing rates (Table 2). d-Sotalol prolonged APD80 in all cells (n = 8, p < 0.05). The change versus control was +21%, +18.5%, +21%, +18%, +20% at 0.5 to 2.5 Hz (p < 0.05). Isoproterenol (n = 8) reduced d-sotalol–induced APD80 prolongation by 47%, 39%, 50%, 51%, and 59% at the

five rates tested (between 0.5 and 2.5 Hz, p < 0.05, Table 2). Figure 1 illustrates the similarity of the effects produced by d-sotalol and sympathetic activation in vivo and in vitro. It is quite evident how adrenergic activation greatly attenuates the prolongation in monophasic action potential duration and in action potential duration produced by d-sotalol. This phenomenon is quantified in Figure 2, where the overall loss in prolongation of repolarization induced by sympathetic activation is 50% and 56%, respectively, in the in vitro and in vivo experimental preparations.

Discussion

The present study, through evidence obtained both in vivo and in vitro and in two different species, demonstrates that sympathetic activation reduces by half the effect of potassium channel blockade on the duration of ventricular repolarization. This finding carries several implications concerning basic cardiac electrophysiology, the observed failure of d-sotalol in preventing ischemia-induced ventricular fibrillation during exercise in dogs after myocardial infarction (7), and the design of clinical trials aimed at reducing the incidence of sudden cardiac death.

Basic cardiac electrophysiology. The combination of the in vitro and in vivo data shows that d-sotalol lengthened action potential duration by a similar amount, ~20%, over a very wide range of pacing rates (from 30 to 220 beats/min). Thus, d-sotalol did not show reverse use dependency (17); that is, its effect was not diminished at the faster heart rates.

Table 2. Effect of Isoproterenol and d-Sotalol on Action Potential Duration In Vitro

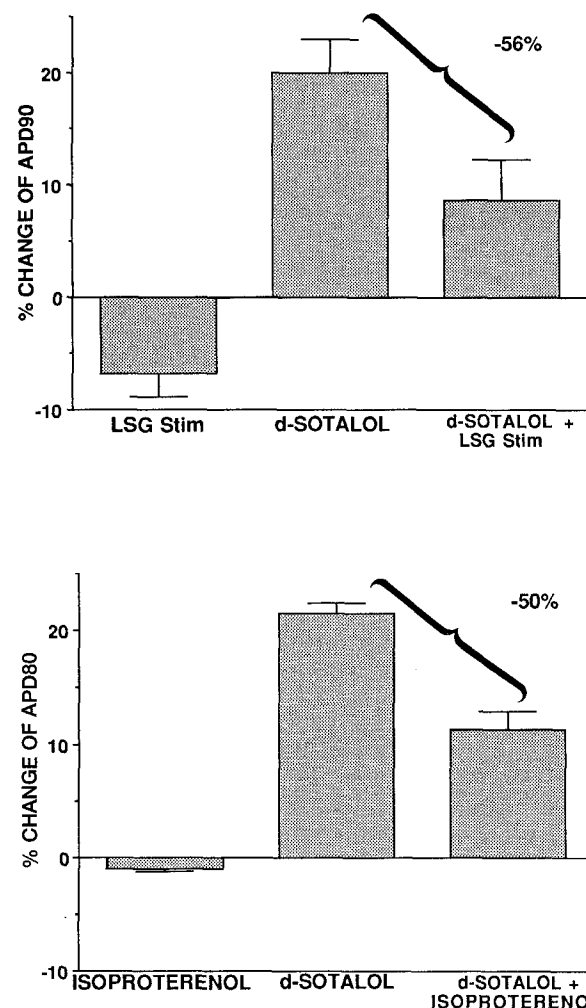| Pacing Rate (Hz)	Action Potential Duration (ms)					ΔAPD80 (%)	
	Control (n = 6)	Isoproterenol (n = 6)	Control (n = 8)	d-Sotalol (n = 8)	d-Sotalol + Isoproterenol (n = 8)	After d-Sotalol	After d-Sotalol + Isoproterenol
0.5	212 ± 28	211 ± 37	199 ± 26	241 ± 27*	219 ± 20*†	21%	10%
1	200 ± 30	198 ± 40	194 ± 29	230 ± 27*	216 ± 22*†	18.5%	11%
1.5	198 ± 22	200 ± 38	191 ± 28	231 ± 28*	211 ± 18*†	21%	10%
2	190 ± 20	195 ± 40	187 ± 26	220 ± 22*	203 ± 18*†	18%	8.5%
2.5	165 ± 8‡	162 ± 21‡	183 ± 27	220 ± 30*	198 ± 21*†	20%	8.2%

*p < 0.05 versus control. †p < 0.05 versus d-sotalol and control. ‡n = 2. ΔAPD80 = change in action potential duration at 80% of repolarization.
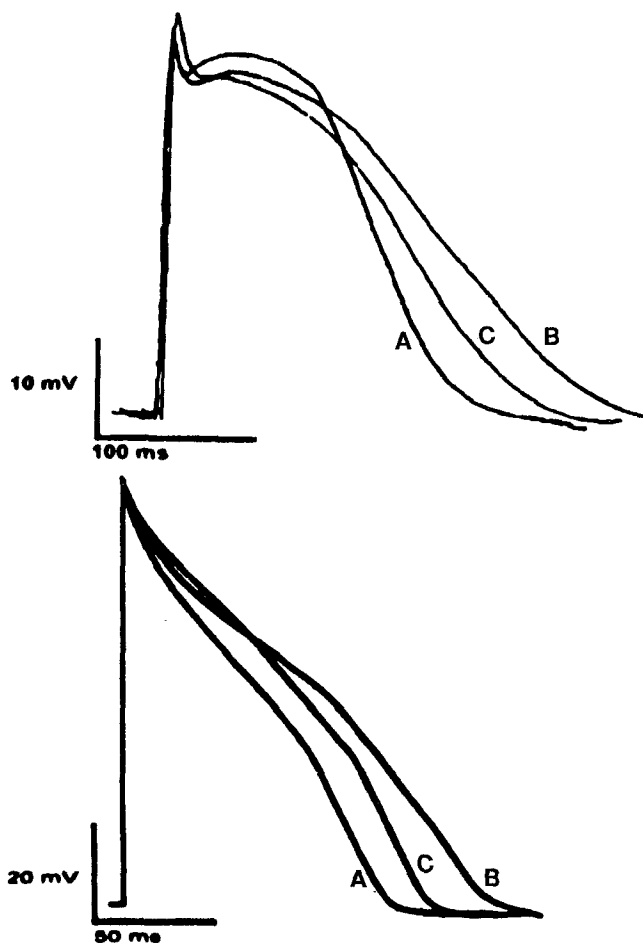
Figure 1. Effect of d-sotalol and adrenergic stimulation on action potential duration. **Top,** Three left ventricular monophasic action potentials in the same dog. **Bottom,** Three action potentials from the same guinea pig ventricular myocyte. A = control conditions; B = after d-sotalol (intravenous administration or addition in the perfusion solution); C = the effect of adrenergic stimulation (left stellate ganglion stimulation or isoproterenol in vitro).

Figure 2. Percent change (mean ± SE) in action potential duration from control conditions induced by d-sotalol and by adrenergic stimulation. **Top,** Effects of left stellate ganglion stimulation (LSG Stim) on monophasic action potential in nine dogs at a pacing rate of 200 beats/min. **Bottom,** Changes observed in eight isolated guinea pig ventricular myocytes with d-sotalol and isoproterenol at a 1.5-Hz pacing frequency. Adrenergic stimulation reduced by 50% the action potential prolongation induced by d-sotalol. APD90, APD80 = action potential duration measured at 90% and 80% of repolarization.

The duration of repolarization was unaffected by isoproterenol in vitro, whereas in vivo left stellate ganglion stimulation slightly shortened repolarization. The in vitro finding is not surprising because in two previous studies (18,19), based on the same isoproterenol concentration used in the present study, a slight prolongation of action potential duration was observed. The 4% to 8% reduction in monophasic action potential duration with stellate ganglion stimulation is consistent with the previous finding by Kuo and Surawicz (20).

After d-sotalol, adrenergic stimulation reduced action potential duration in almost all cases. With the pure I$_{kr}$ blocker E-4031, Sanguinetti et al. (11) observed that isoproterenol produced a variable response in control conditions (action potential duration shortening or prolongation), but that it always shortened action potential duration after E-4031. Independent of the mechanisms involved, the fact that at a longer action potential duration adrenergic activation is more likely to result in a shortening of action potential duration, and thus of

refractoriness, has obvious implications for the antiarrhythmic effect of potassium channel blockers.

These considerations have to be placed in the context of the inability of d-sotalol to prevent lethal arrhythmias caused by transient myocardial ischemia during exercise in conscious dogs with a healed myocardial infarction (7). Indeed, protection from ventricular fibrillation was observed in only 1 (10%) of 10 dogs treated with d-sotalol; this observation is in contrast to the protection of 6 (67%) of 9 of the same dogs treated with the racemic compound d,l-sotalol (7).

In the present study both the relative (i.e., the percent value) and the absolute prolongation achieved by d-sotalol were markedly attenuated by beta-adrenergic stimulation. The relative prolongation of repolarization by d-sotalol was similar

in control conditions and in the sympathetic stimulated state; however, from the findings in the conscious dogs with a previous myocardial infarction (7), we now know that the antiarrhythmic efficacy of d-sotalol is substantially attenuated by sympathetic activation. It is reasonable to postulate that this failure may be due to the interaction between sympathetic stimulation and the so-called class III effect of d-sotalol, that is, the prolongation of refractoriness, which is a direct consequence of the prolongation of action potential duration. Sympathetic activation interferes with the achievement of an *adequate* prolongation of ventricular refractoriness. This is because the absolute value, rather than the relative change, of the refractory period produced by the drug best reflects its ability to suppress reentrant excitation.

The results of this study may be explained according to Sanguinetti et al. (11), who documented that the slow component of I_k, I_{ks}, not blocked by traditional potassium channel blockers such as d-sotalol, is enhanced by isoproterenol. In guinea pig ventricular myocytes at the plateau phase of a normal action potential, I_{kr} and I_{ks} are quantitatively similar. Thus, blockade of I_{kr} alone is likely to affect only 50% of I_k. Given the marked effect of isoproterenol on I_{ks}, in conditions of high sympathetic activity I_{ks} may annul the effect of I_{kr} blockade on action potential duration. These results indicate that a correct analysis of basic cardiac electrophysiology can no longer ignore the importance of the interaction between antiarrhythmic drugs and autonomic activity. Specifically, the activation or block of an ionic channel may be potentiated or drastically reduced by autonomic mediators.

Antifibrillatory efficacy of d-sotalol. The present findings help to explain the important failure of d-sotalol to prevent ventricular fibrillation due to acute myocardial ischemia in conditions of elevated sympathetic activity in conscious dogs with a healed myocardial infarction (7,21,22). Previous experiments in anesthetized rabbits had indicated that the action potential prolongation produced by d,l-sotalol gradually disappears during acute myocardial ischemia. However, d-sotalol prevented ventricular fibrillation in conscious dogs with a 4- to 7-day old myocardial infarction exposed to a permanent occlusion of the left circumflex coronary artery (9). In that model the occlusion develops progressively due to a growing endoluminal thrombus and does not elicit powerful sympathetic reflexes. In our own model (8), the high sympathetic activity and fast heart rate probably contribute to activate I_{ks} and, to judge from the present findings, are likely to create a critical reduction of the electrophysiologic effects of d-sotalol so that ventricular fibrillation cannot be prevented.

Clinical implications. The traditional design of clinical trials related to sudden death is based on the implicit, and incorrect, assumption that all enrolled patients will die because of the same mechanism. However, the two main mechanisms of death among postmyocardial infarction patients appear to involve either a substrate-dependent ventricular tachycardia-fibrillation or an ischemia-related ventricular fibrillation favored by increases in sympathetic activity (23). I_{kr} blockers are probably very effective against the first mechanism and repre-

sent a rational choice for prevention of reentrant tachy-arrhythmias with a short excitable gap (6). Conversely, the present data suggest a lesser degree of protection in conditions of high sympathetic activity. This information may be relevant to the design of clinical trials, such as SWORD (Survival With ORal D-sotalol) (24), because it suggests that potassium channel blockers should be primarily tested in those patients more likely to die because of the first arrhythmogenic mechanism; they may be identified by the presence of a depressed left ventricular function and of late potentials. Conversely, it may be wise not to expect a large beneficial effect in those patients more likely to die because of the second arrhythmogenic mechanism; they may be identified by the presence of a depressed heart rate variability and baroreflex sensitivity (25). Such a mechanism-oriented approach to the design of clinical trials might avoid a situation in which the simultaneous inclusion of patients who may and may not be protected by the study drug might obscure an otherwise statistically significant protection, and lead to early termination of the trial (26) on the basis of negative results. The final goal remains the identification of the most appropriate therapy for each patient, on the basis of the most likely arrhythmogenic mechanism (6).

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