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# Prevention of ventricular fibrillation by dextrorotatory sotalol in a conscious canine model of sudden coronary death

The antiarrhythmic and antifibrillatory actions of the dextrorotatory isomer of sotalol, administered in a multiple-dose regimen, were evaluated in conscious dogs 3 to 5 days after anterior myocardial infarction. The intravenous administration of d-sotalol, four 8 mg/kg doses over a 24-hour treatment period, suppressed the induction of ventricular tachycardia by programmed electrical stimulation in six of nine dogs tested, slowed the rate of the induced tachyarrhythmia in two of the remaining three dogs, and provided significant protection (5 of 8 d-sotalol vs 0 of 8 vehicle control) against the development of ventricular fibrillation in response to ischemia at a site distant to a previous myocardial infarction. Increases in ventricular myocardial refractoriness and in QT<sub>c</sub> and paced QT intervals suggest that class III electrophysiologic actions contribute to the antiarrhythmic properties of dextrorotatory sotalol in this animal model. The degree of beta-adrenergic receptor blockade produced by d-sotalol in this dose regimen was negligible. These findings suggest the potential utility of d-sotalol in the prevention of ventricular tachycardia and ventricular fibrillation in the setting of myocardial infarction, particularly when beta-adrenergic receptor blockade is undesirable or contraindicated. (AM HEART J 109:949, 1985.)

Joseph J. Lynch, Ph.D., Lawrence A. Coskey, B.S., Daniel G. Montgomery, B.S., and Benedict R. Lucchesi, Ph.D., M.D. *Ann Arbor, Mich.*

Recently, considerable attention has focused on the use of class III antiarrhythmic agents such as amiodarone<sup>1-3</sup> and bretylium<sup>4-6</sup> for the management of patients with malignant ventricular tachycardia (VT) or ventricular fibrillation. The characteristic electrophysiologic property of this relatively novel class of antiarrhythmic agents is a selective prolongation of cardiac action potential duration, resulting in an increase in myocardial refractoriness.<sup>7</sup> An increase in myocardial refractoriness presumably underlies the antiarrhythmic and antifibrillatory actions of the class III agents through a suppression or termination of reentrant circuits by interposing refractory tissue to an advancing wave of depolarization.<sup>8</sup>

Racemic sotalol (d,l-4-(2-isopropylamino-1-hy-

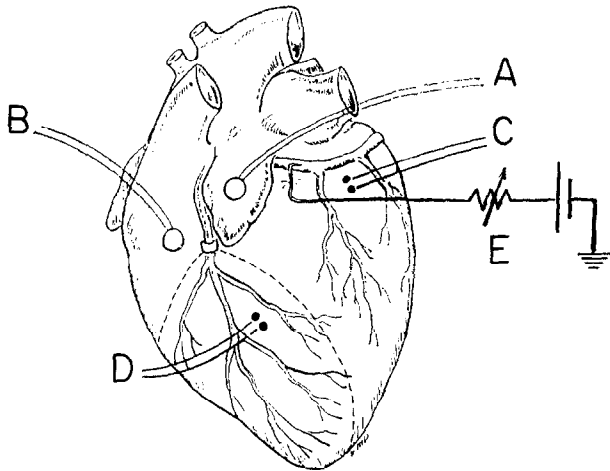
droxyethyl)-methanesulfonamide, MJ1999), which initially was introduced as a beta-adrenergic receptor antagonist lacking intrinsic sympathomimetic and membrane-stabilizing activities,<sup>9,10</sup> has been shown to prolong the cardiac action potential duration and increase myocardial refractoriness in vitro<sup>11,12</sup> and in vivo.<sup>13-17</sup> A prolongation in ventricular refractoriness has been proposed to underlie the antiarrhythmic and antifibrillatory actions of d,l-sotalol in experimental postinfarction canine models<sup>18,19</sup> and clinically in patients with recurrent life-threatening VT.<sup>20</sup> Recently, this laboratory has demonstrated that both the resolved levorotatory (l) isomer of sotalol (the "active" beta-blocking form of sotalol; the optical activity ratio l/d for beta blockade having been reported to be 44<sup>21</sup>) and the dextrorotatory (d) isomer (which would be relatively devoid of beta-blocking activity) acutely suppress the induction of VT by programmed ventricular stimulation and equieffectively increase ventricular refractoriness in conscious postinfarction dogs.<sup>22</sup> Administered as acute pretreatments, however, neither optical isomer provided statistically significant protection, as assessed by 24-hour survival, in a conscious canine model of sudden death in which

From the Department of Pharmacology, The University of Michigan Medical School.

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Reprint requests: Benedict R. Lucchesi, Ph.D., M.D., Department of Pharmacology, M6322 Medical Science Building I, The University of Michigan Medical School, Ann Arbor, MI 48109.



**Fig. 1.** Conscious canine model of sudden coronary death. On the day of surgical preparation, anterior myocardial ischemic injury (broken lines) is produced by 2-hour occlusion of the left anterior descending coronary artery, followed by reperfusion through a critical stenosis. An epicardial bipolar electrode (A) is sewn onto the left atrial appendage for atrial pacing, and a plunge bipolar electrode (B) is inserted into the interventricular septum, adjacent to the site of occlusion, for the determination of ventricular excitation threshold and effective refractory period, as well as for the delivery of programmed ventricular extrastimuli. Plunge bipolar electrodes are inserted into normal, noninjured myocardium (C) and into potentially infarcted myocardium (D) for recording of local activation and determination of ventricular activation times. The bared tip of an insulated silver wire (E) is inserted into the lumen of the left circumflex coronary artery, and the wire is sutured onto the surface of the heart. Dogs are returned to the laboratory for electrophysiologic monitoring in the conscious, unanesthetized state, 3 to 5 days after surgical preparation.

ventricular fibrillation occurred suddenly and reliably in response to ischemia at a site distant from an area of previous myocardial infarction.<sup>22</sup>

The purpose of the present investigation, therefore, was to assess the antifibrillatory actions of dextrorotatory sotalol, the "non beta-blocking" sotalol isomer, administered in a multiple-dose pretreatment regimen, in the aforementioned conscious postinfarction dog model of sudden coronary death. The essential experimental features of this canine sudden death model are illustrated in Fig. 1. The beta-adrenergic receptor-blocking actions of d-sotalol in this protocol, as well as the effects of the d-isomer upon the initiation of ventricular tachyarrhythmias by programmed stimulation, were also determined. The results of this investigation demonstrate that in a multiple-dose pretreatment regimen, dextrorotatory sotalol suppresses the induction of VT and provides significant protection against the development of ventricular fibrillation in response

to acute ischemia in conscious postinfarction dogs. These findings suggest that the dextrorotatory isomer of sotalol may be useful in the prevention of lethal ventricular arrhythmias in the setting of myocardial ischemic injury.

## METHODS

**Surgical preparation.** Male mongrel dogs (14.0 to 18.0 kg) were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. The dogs were ventilated with room air by means of a cuffed endotracheal tube and a Harvard respirator. Using aseptic technique, the left external jugular vein and left common carotid artery were isolated and cannulae were inserted. A left thoracotomy was performed between the fourth and fifth ribs. The pericardium was opened and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was isolated at the tip of the left atrial appendage, and the left circumflex coronary artery was isolated approximately 1 cm from its origin. A 19- or 20-gauge hypodermic needle was placed parallel to the left anterior descending coronary artery and a suture was passed around both the vessel and the needle. The suture was tied securely and the needle was withdrawn, producing a critical stenosis. The artery was then occluded by means of a snare formed from a loop of silicone rubber tubing (Retracto-Tape) passed through a polyethylene tube. Blood flow through the left anterior descending coronary artery was restored after 2 hours.

An epicardial bipolar electrode (1 mm diameter silver electrodes embedded 3 mm apart in acrylic) was sutured to the left atrial appendage for atrial pacing. A bipolar plunge electrode (25-gauge, insulated, stainless steel wire, 5 mm in length, 2 mm apart) was sutured into the interventricular septum adjacent to the right ventricular outflow tract for the determination of ventricular excitation threshold and ventricular effective refractory period and for the introduction of ventricular extrastimuli during programmed stimulation. Two short (2 to 3 mm) stainless steel bipolar plunge electrodes were used for measurement of ventricular activation times. One short bipolar electrode was implanted in the distribution of the left anterior descending coronary artery distal to the site of occlusion (IZ = infarct zone), while a second was implanted in the left circumflex coronary artery distribution (NZ = normal zone). A 3 mm section of bared, insulated, 30-gauge silver wire was inserted through the wall of the vessel into the lumen of the left circumflex coronary artery and was sutured in place on the surface of the heart. Silver disc electrodes were implanted subcutaneously for ECG monitoring. The surgical incision was closed and the animals were allowed to recover from surgical anesthesia.

**Programmed electrical stimulation in the conscious dog.** Programmed electrical stimulation was performed between days 3 and 5 after anterior myocardial infarction. Animals were studied while conscious, unanesthetized, and resting comfortably in a sling. ECG intervals and electrophysiologic parameters were determined immediately

before programmed electrical stimulation testing was initiated. ECG intervals were measured during sinus rhythm. A corrected QT interval ( $QT_c = QT$  in msec/(R-R in sec)<sup>1/2</sup>) was determined during sinus rhythm, while a paced QT interval was determined during atrial pacing (2.5 Hz). Ventricular excitation thresholds, effective refractory periods, and activation times were determined during atrial pacing (2.5 Hz). The ventricular excitation threshold was defined as the minimum voltage required to produce a conducted ventricular complex at a stimulus duration of 4 msec delivered 300 msec after the R wave of the lead II ECG. The ventricular effective refractory period was the longest R-to-stimulus interval at which a 2× threshold stimulus (4 msec duration) failed to produce a conducted ventricular impulse. Ventricular activation time, the interval between the Q wave of the lead II ECG and the largest deflection of the local ventricular electrogram (Q-EG), was measured on a Tektronix model 5111 oscilloscope.

During the programmed electrical stimulation protocol, premature ventricular stimuli (4 msec duration, 2× threshold) were introduced into the interventricular septum by means of a Grass model S-88 stimulator and a Grass model SIU-5 stimulus isolation unit. Single ( $S_2$ ), double ( $S_2S_3$ ), and then triple ( $S_2S_3S_4$ ) premature ventricular stimuli were introduced. Single ventricular extrastimuli were introduced during atrial pacing at  $S_1$ - $S_2$  coupling intervals decreasing from 350 msec until ventricular refractoriness occurred. Thereafter, double and triple ventricular extrastimuli were introduced during sinus rhythm at  $S_2$ - $S_3$  and  $S_2$ - $S_3$ - $S_4$  coupling intervals of 182, 167, 154, 142, 133, and 125 msec. Previous work has shown that this method fails to produce ventricular dysrhythmias in sham-operated animals without previous myocardial ischemic injury.<sup>23</sup>

Two groups of postinfarction dogs were subjected to programmed stimulation testing. Dogs assigned to the vehicle control group were subjected to electrophysiologic testing and programmed stimulation before and after treatment with normal saline solution: four 10 ml intravenous infusions of 10 minutes duration each, one infusion every 8 hours, over a total treatment period of 24 hours. After determination of baseline electrophysiologic values and pretreatment programmed stimulation testing, dogs in the experimental drug treatment group were subjected to repeat programmed stimulation testing after *d*-sotalol administration: four 8 mg/kg intravenous infusions, each infused in a volume of 10 ml over a period of 10 minutes, one infusion every 8 hours, over a total treatment period of 24 hours. After posttreatment programmed stimulation testing and assessment of beta-adrenoceptor blockade by isoproterenol infusion, dogs in the vehicle (normal saline solution) and *d*-sotalol treatment groups immediately were entered into the protocol for sudden coronary death.

All dogs in this evaluation were assigned randomly to their respective treatment groups before pretreatment electrophysiologic study. Only dogs which were susceptible to the reproducible induction of nonsustained or

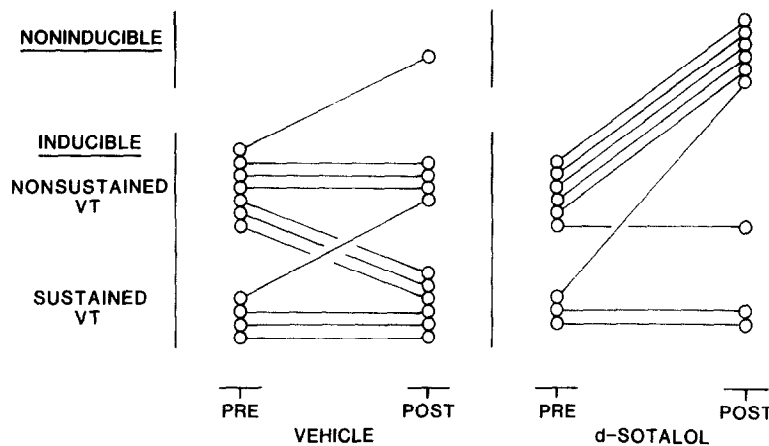
sustained VT by pretreatment programmed stimulation were included in this study. VTs were defined as "nonsustained" if, by using the protocol described previously, five or more repetitive ventricular responses were initiated reproducibly but terminated spontaneously. Ventricular tachyarrhythmias were defined as "sustained" if they persisted for at least 30 seconds or, in the event of hemodynamic compromise, they required ventricular burst pacing for their termination. If VT degenerated into ventricular fibrillation, the animal was excluded from the study to avoid the potentially confounding influence of occasionally prolonged resuscitative efforts on the outcome of the second phase of the investigation. If nonsustained VT could be initiated reproducibly, more aggressive attempts to induce sustained tachycardia were not made. Animals responding with less than five nonstimulated complexes during the entire protocol were designated as noninducible. Dogs were entered randomly into the programmed stimulation protocol until an *n* of 8 was attained in the sudden coronary death protocol (below). Due to technical failures associated with this latter protocol, an *n* of >8 was realized for each of the treatment groups for the programmed stimulation protocol.

**In vivo assessment of beta-adrenergic receptor blockade.** The sinus heart rate and systemic diastolic blood pressure responses to the rapid intravenous infusion of 0.2 µg/kg isoproterenol were determined immediately before and after the appropriate 24-hour treatment period in vehicle and drug treatment groups. The dose of isoproterenol had been determined to approximate the ED50 dose for the aforementioned responses in untreated postinfarction dogs. In this evaluation, the postinfarction dogs were challenged with one infusion of isoproterenol in order to minimize the induction of malignant ventricular arrhythmias by repeated catecholamine administration during this phase of the evaluation.

**Conscious canine model of sudden coronary death—ventricular fibrillation in response to ischemia at a site remote from previous myocardial infarction.** After completion of final posttreatment programmed ventricular stimulation testing, an anodal direct current of 150 µA was applied to the intimal surface of the left circumflex coronary artery via the previously inserted silver wire electrode. The lead II ECG was recorded directly onto a Grass polygraph or was recorded at preset intervals by a programmable cardiocassette recorder.

Upon completion of the experiment at 24 hours of electrical stimulation or upon development of ventricular fibrillation, the heart was excised and thrombus mass within the left circumflex coronary artery was determined after removal by careful dissection. The heart was cut into 1 cm thick transverse sections which were placed in 0.5% triphenyltetrazolium chloride in 0.01M phosphate buffer (pH 7.4). Infarct size was quantitated gravimetrically with the aid of the differential histochemical staining technique.

**Drug administration.** The resolved dextrorotatory isomer of sotalol (Mead Johnson Laboratories) was provided as a monohydrochloride salt. Indicated dosages reflect



**Fig. 2.** Effects of administration of saline solution vehicle, 10 ml intravenously every 8 hours four times (*left*,  $n = 11$ ), or d-sotalol, 8 mg/kg intravenously every 8 hours four times (*right*,  $n = 9$ ), upon the responses of postinfarction dogs to programmed ventricular stimulation. In these figures, each symbol represents one animal, with the nature of the response of each animal to programmed stimulation listed on the Y-axis. For each treatment group, the response of the animals to programmed stimulation both before (*PRE*) and after (*POST*) the appropriate treatment is depicted. Before treatment in both groups, the introduction of one to three ventricular extrastimuli (see Methods for stimulation protocol) elicited nonsustained or sustained ventricular tachycardia (VT) in each of the postinfarction dogs. *Right*, Administration of d-sotalol (*POST*) suppressed the induction of VT in six of nine dogs tested in this study (i.e., six dogs were rendered noninducible). *Left*, In the vehicle control group (*POST*), 10 of 11 dogs remained inducible after 24-hour administration of saline solution.

**Table I.** Programmed ventricular stimulation

Parameter	Vehicle ( $n = 11$ )	d-Sotalol ( $n = 9$ )
Pretreatment VT cycle length (msec)	$173 \pm 9$	$154 \pm 19$
Posttreatment VT cycle length (msec)	$190 \pm 15^*$	$253 \pm 35^\dagger$
Incidence of prolongation ( $\geq 20\%$ ) of VT cycle length with treatment	2/10*	2/3†
Incidence of noninducibility with treatment	1/11	6/9‡
Incidence of spontaneous ventricular ectopy with treatment	0/11	4/9‡
Underlying anterior infarct size (% of left ventricle)	$25.4 \pm 3.6$	$22.5 \pm 4.1$

\* $N = 10$ , with one dog noninducible.

† $N = 3$ , with six dogs noninducible; the appropriate pretreatment cycle lengths for this subset of three dogs are  $211 \pm 42$  msec.

‡ $p < 0.05$  vs vehicle-treated group.

dosages of the base compound. Normal (0.9% aqueous) saline solution was used as a vehicle throughout.

**Statistical analysis.** For all evaluations, data are expressed as mean  $\pm$  SEM. Pre- and posttreatment values within a given treatment group were compared by paired Student's *t* test. Differences between treatment groups were analyzed by unpaired Student's *t* test or by Fisher's exact test when appropriate. For all comparisons, a *p* value of less than 0.05 was the criterion for statistical significance.

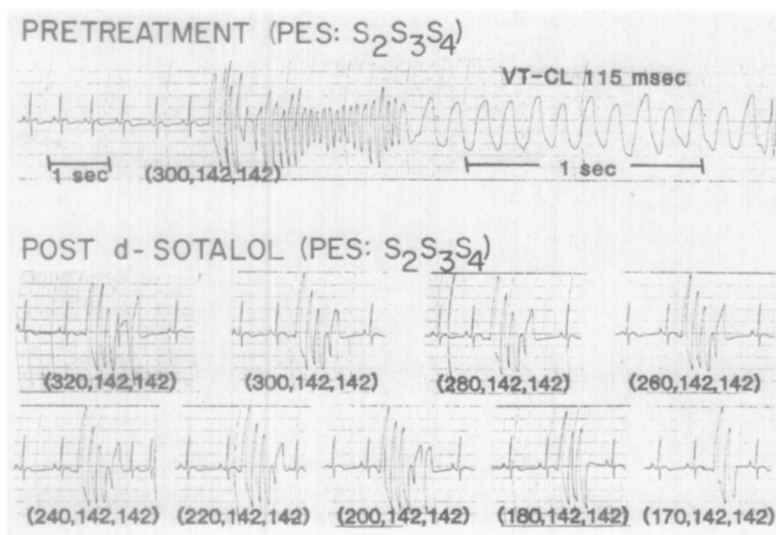
## RESULTS

Twenty-eight conscious dogs were subjected to programmed ventricular stimulation 3 to 5 days

after anterior myocardial infarction. Six dogs were found to be noninducible before treatment and were entered into an alternate study. Two dogs responded to programmed stimulation with ventricular fibrillation and were not resuscitated. The remaining 20 dogs, randomly preassigned to the vehicle ( $n = 11$ , 10 ml of 0.9% aqueous saline intravenously every 8 hours, four administrations over 24 hours) or d-sotalol ( $n = 9$ , 8 mg/kg intravenously every 8 hours, four doses over 24 hours) treatment groups, responded to pretreatment programmed stimulation with reproducible nonsustained or sustained VTs. The antiarrhythmic and electrophysiologic responses of the vehicle- and d-sotalol-treated animals to their respective interventions are presented below.

**Programmed electrical stimulation.** The responses of postinfarction dogs to programmed stimulation, before and after d-sotalol or vehicle treatment, are summarized graphically in Fig. 2 and are characterized in Table I. Neither the cycle lengths of the induced pretreatment tachycardias nor the sizes of the underlying anterior infarcts varied significantly between the two treatment group (Table I).

The administration of d-sotalol in this protocol suppressed the induction of ventricular tachyarrhythmia by programmed stimulation in six of nine dogs tested and furthermore increased the cycle length (reduced the rate) of the induced tachyarrhythmia in two of the three remaining animals (Fig.



**Fig. 3.** Programmed electrical stimulation on a conscious postinfarction dog before (*PRETREATMENT*, upper panel) and after (*POST d-SOTALOL*, lower panels) administration of 8 mg/kg intravenous d-sotalol every 8 hours, four doses over 24 hours. Before the drug, introduction of three ventricular extrastimuli ( $S_2S_3S_4$ ) at critical coupling intervals elicits a sustained ventricular tachycardia (VT) with a cycle length (*VT-CL*) of 115 msec. After d-sotalol administration, the introduction of ventricular extrastimuli in the same range of coupling intervals elicits only one or two ventricular complexes in response, thus rendering the animal noninducible. Numbers in parentheses indicate the  $S_1$ - $S_2$ ,  $S_2$ - $S_3$ , and  $S_3$ - $S_4$  coupling intervals in msec. Depicted ECG is lead II.

**Table II.** ECG and electrophysiologic responses

Parameter	Vehicle		d-Sotalol	
	Before	After	Before	After
Heart rate (bpm)	118 ± 5	106 ± 8	123 ± 7	99 ± 4*
Mean arterial pressure (mm Hg)	78 ± 4	80 ± 4	77 ± 3	77 ± 2
PR interval (msec)	119 ± 4	121 ± 4	115 ± 4	124 ± 4
QRS interval (msec)	59 ± 1	59 ± 1	60 ± 1	58 ± 1
QT <sub>c</sub> interval (msec) (sec) <sup>-1/2</sup>	301 ± 11	295 ± 10	304 ± 12	318 ± 8*
Paced QT interval (msec)	203 ± 6	208 ± 4	199 ± 7	225 ± 6*
Ventricular excitation threshold (V)	2.0 ± 0.2	1.9 ± 0.2	2.1 ± 0.2	2.6 ± 0.4
Ventricular refractory period (msec)	155 ± 5	150 ± 5	148 ± 4	164 ± 5*
Ventricular activation time—normal zone (msec)	18.8 ± 1.8	18.8 ± 2.3	16.6 ± 1.9	17.1 ± 1.7
Ventricular activation time—infarct zone (msec)	26.3 ± 3.4	27.3 ± 2.7	22.2 ± 1.3	22.9 ± 1.4

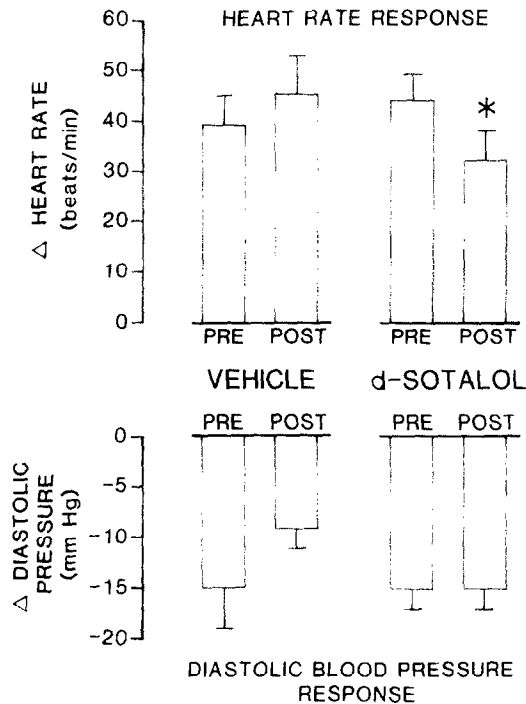
N = 9 to 11.

\**p* < 0.05 after vs before.

2, Table I). Dextrorotatory sotalol appeared to be most effective in suppressing the induction of tachyarrhythmias in those dogs characterized by pretreatment tachycardias of short cycle lengths (pretreatment tachycardia cycle length of d-sotalol “protected” dogs vs “unprotected” dogs: 125 ± 7 msec vs 211 ± 42 msec) and/or requiring closely coupled extrastimuli for arrhythmia induction. In contrast, 24-hour vehicle treatment had a minimal effect upon the induction of ventricular tachyarrhythmias by programmed ventricular stimulation (Fig. 2, Table I). The overall rate of complete

effectiveness (suppression of tachycardia induction) was significantly greater with d-sotalol (six of nine, 67%) than with saline solution vehicle (1/11, 9%; *p* < 0.05).

The experiment depicted in Fig. 3 illustrates the suppression of electrically induced VT by d-sotalol. In this example, before drug administration (*upper*) the introduction of three ventricular extrastimuli at critical coupling intervals elicits a sustained ventricular tachyarrhythmia with a cycle length of 115 msec. After 24-hour d-sotalol treatment (*lower*), the introduction of three extrastimuli in the same range



**Fig. 4.** In vivo assessment of beta-adrenergic receptor blockade: Sinus heart rate (*upper*) and systemic diastolic blood pressure (*lower*) responses of d-sotalol (*right*)- and vehicle (*left*)-treated postinfarction dogs to rapid infusion of 0.2  $\mu\text{g}/\text{kg}$  isoproterenol were determined immediately before (*PRE*) and after (*POST*) their respective 24-hour treatment periods. d-Sotalol treatment (*right*) slightly but significantly reduced the positive chronotropic response to isoproterenol, while the diastolic pressure response in d-sotalol-treated dogs was unaltered. Vehicle treatment (*left*) did not significantly alter heart rate or blood pressure response to isoproterenol.  $n = 9-11$ ; \* $p < 0.05$  POST vs PRE.

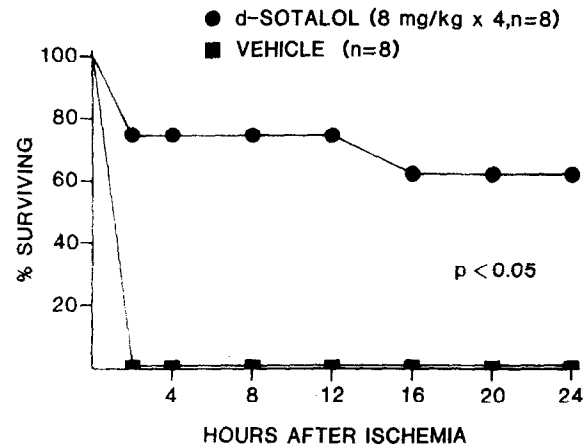
**Table III.** Conscious canine model of sudden death

Parameter	Vehicle ( $n = 8$ )	d-Sotalol ( $n = 8$ )
Increase in heart rate upon ST segment change (% of preischemic rate)	$+41 \pm 5$	$+32 \pm 10$
Incidence of "sudden" ventricular fibrillation upon ischemia	7/8	1/8†
24-Hour survival rate	0/8	5/8†
Infarct size (% of left ventricle)		
Left anterior descending	$21.7 \pm 3.1$	$18.9 \pm 2.9$
Left circumflex	--	$23.3 \pm 3.9$ ( $n = 7$ )
Thrombus mass (mg)	$5.3 \pm 1.5$	$11.1 \pm 2.6$

\*Incidence of ventricular fibrillation within 60 minutes of ischemia.  
† $p < 0.05$  vs vehicle-treated group.

of coupling intervals elicits only one or two ventricular complexes in response, thereby rendering the animal noninducible.

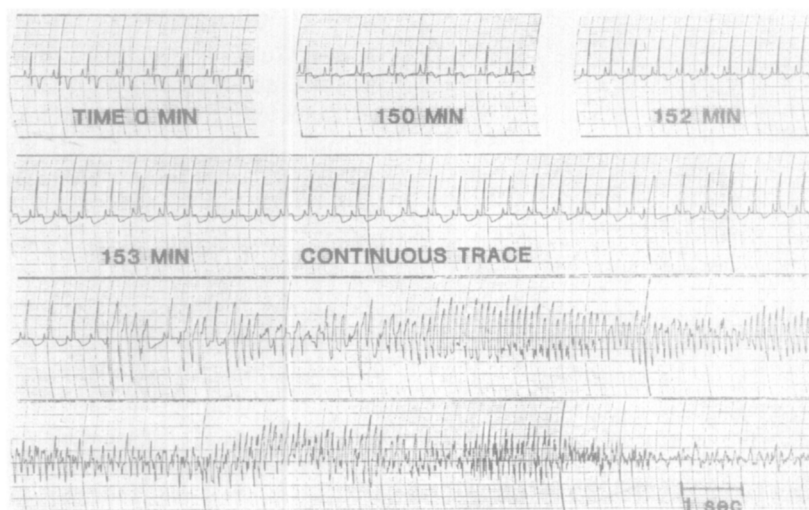
**Electrophysiologic responses.** Table II summarizes



**Fig. 5.** Survival rates of d-sotalol- and saline-pretreated dogs after development of posterolateral ischemia following left circumflex intimal injury. At 24 hours after the development of posterolateral ischemia in the presence of an anterior myocardial infarct, d-sotalol (8 mg/kg intravenously every 8 hours, four doses over 24 hours) significantly increased ( $p < 0.05$ ) survival compared to saline-treated vehicle control dogs.

the electrophysiologic, ECG, heart rate, and systemic blood pressure responses of postinfarction dogs to 24-hour vehicle or d-sotalol treatment. d-Sotalol treatment significantly increased the ventricular effective refractory period but did not alter ventricular activation (conduction) times or excitation threshold. The administration of d-sotalol also prolonged both the  $QT_c$  interval and the paced  $QT$  interval while the PR and QRS intervals were unaltered. Both the d-sotalol and vehicle posttreatment heart rates were less than their respective pretreatment values, with the d-sotalol posttreatment value significantly less than the pretreatment value. The magnitudes of the reduction in heart rate for the two treatment groups, however, did not differ significantly. Vehicle administration did not significantly alter electrophysiologic parameters or ECG intervals (Table II). Neither d-sotalol nor vehicle treatment significantly altered mean arterial pressure in the postinfarction dogs (Table II).

**Beta-adrenergic receptor blockade.** Fig. 4 summarizes the heart rate and systemic diastolic blood pressure responses of d-sotalol- and vehicle-treated dogs, immediately before and after their respective 24-hour treatments, to the rapid intravenous infusion of 0.2  $\mu\text{g}/\text{kg}$  isoproterenol. d-Sotalol administration slightly but significantly reduced the positive chronotropic response of postinfarction dogs to the catecholamine, while the diastolic blood pressure-lowering response was unaltered. Vehicle administration altered neither the heart rate nor blood pressure response to isoproterenol (Fig. 4). Neither



**Fig. 6.** Ventricular fibrillation in a vehicle-pretreated conscious dog in response to the development of posterolateral ischemia in the presence of an anterior myocardial infarct. An anodal current of  $150 \mu\text{A}$  was applied to the intimal surface of the left circumflex (LCX) coronary artery at time 0. ECG alterations reflecting acute ischemia (increasing R wave amplitude, reflex tachycardia) were observed at 152 minutes of current, followed rapidly by the development of ventricular ectopy, tachycardia, and ventricular fibrillation at 153 minutes of current. Depicted ECG is lead II.

*d*-sotalol nor vehicle pretreatment blunted the sympathetically mediated reflex tachycardic response to the development of acute posterolateral ischemia in the postinfarction dogs (Table III).

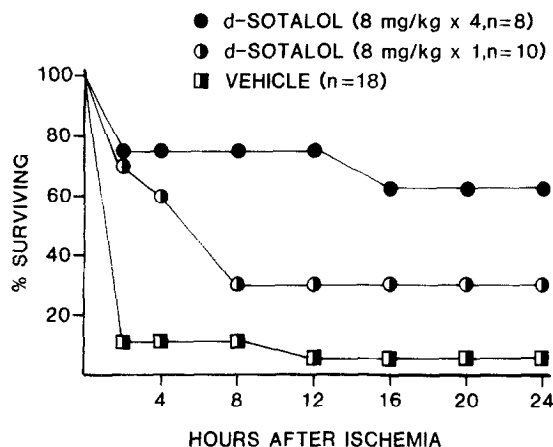
**Spontaneous ventricular ectopic activity.** Transient episodes of spontaneous ventricular ectopic activity were observed in four of nine *d*-sotalol-treated dogs during or immediately after drug infusion. These episodes of ventricular ectopy were suppressed readily by atrial pacing at a rate slightly exceeding that of the sinoatrial rate. The occurrence of ventricular ectopy did not appear to correlate with the degree of QT prolongation in the *d*-sotalol-treated animals, as the absolute increase in paced QT interval in the ectopic animals ( $+20 \pm 6$  msec) was actually slightly (but not significantly) less than the increase observed in nonectopic dogs ( $+35 \pm 8$  msec). Episodes of spontaneous ventricular ectopy were not observed during or after vehicle infusion.

**Conscious canine model of sudden coronary death.** Immediately after the posttreatment assessment of the abilities of *d*-sotalol or vehicle to influence the induction of VT by programmed electrical stimulation, an anodal current of  $150 \mu\text{A}$  was applied to the intimal surface of the left circumflex coronary artery in each of eight dogs in the two treatment groups. The responses of the two treatment groups to left circumflex intimal stimulation are summarized in Table III. The times to the development of ECG evidence of posterolateral ischemia in the two groups were comparable, and the reflex tachycardic responses to posterolateral ischemia as well as the

masses of the underlying anterior infarcts did not differ significantly between the two treatment groups (Table III).

The responses of *d*-sotalol- and vehicle-pretreated dogs to posterolateral ischemia in the presence of a previous anterior infarction are compared graphically in the survival curves depicted in Fig. 5. Pretreatment with vehicle afforded minimal protection against the development of sudden ventricular fibrillation in this evaluation. In the vehicle-treated group, seven of eight dogs developed ventricular fibrillation within  $13 \pm 6$  minutes of the ECG manifestation of posterolateral ischemia as assessed by alterations in the lead II ECG recording. The one remaining animal died of ventricular fibrillation 108 minutes after the onset of regional ischemia. An example of sudden ventricular fibrillation in the vehicle treatment group is shown in Fig. 6.

Pretreatment with *d*-sotalol (8 mg/kg intravenously every 8 hours, four doses over 24 hours) provided significant protection against the development of ventricular fibrillation occurring in response to posterolateral ischemia in postinfarction dogs (Fig. 5, Table III). In the *d*-sotalol-treated group, only one of eight dogs died of ventricular fibrillation within the first 60 minutes of ischemia and five dogs survived the entire 24-hour protocol. Late arrhythmic deaths and 24-hour survivals in this treatment group displayed histochemical evidence of myocardial infarction in the left circumflex distribution, a rare finding in vehicle-treated animals because of the rapidity of the development of ventricular fibril-



**Fig. 7.** Cumulative survival rates of multiple-dose d-sotalol (four 8 mg/kg intravenous doses over 24 hours), single-dose d-sotalol (one 8 mg/kg intravenous dose),<sup>22</sup> and saline vehicle-pretreated dogs after the development of posterolateral ischemia in the presence of an anterior myocardial infarction. These data indicate an enhanced protection with multiple-dose vs single-dose d-sotalol pretreatment in this sudden death model.

lation in unprotected animals. d-Sotalol-pretreated survivors in this evaluation, therefore, possessed both anterior and posterolateral infarcts cumulatively comprising approximately 40% of the total left ventricular mass (Table III) and were fully ectopic at 24 hours after the onset of posterolateral ischemia. Cumulative survival rates of multiple-dose d-sotalol (four 8 mg/kg intravenous doses over 24 hours), single-dose d-sotalol (one 8 mg/kg intravenous dose)<sup>22</sup>, and saline solution, vehicle-pretreated postinfarction dogs in this sudden death model are compiled and presented in Fig. 7. These cumulative survival data indicate an enhanced protection with multiple-dose vs single-dose d-sotalol pretreatment in this conscious canine model of sudden coronary death.

## DISCUSSION

### Conscious canine model of sudden coronary death.

The conscious postinfarction canine model used in this study has been developed in order to assess the potential efficacy of pharmacologic interventions in protecting against sudden coronary death.<sup>23</sup> As utilized by this laboratory, the postinfarction canine model is susceptible to the reproducible induction of presumably reentrant ventricular tachyarrhythmias by programmed ventricular stimulation, and suddenly and reliably responds to an acute ischemic event at a site distant from an area of previous myocardial infarction with the development of ventricular fibrillation.<sup>23,24</sup> Clinically, over one half of all sudden deaths occur in subjects with previous myo-

cardial infarction.<sup>25-28</sup> Furthermore, ventricular tachyarrhythmias may be induced by programmed ventricular stimulation in the majority of patients resuscitated from sudden death,<sup>25,27-29</sup> thereby indicating the presence of an electrically vulnerable myocardial substrate which may entertain a potentially lethal arrhythmia, and providing a potential means by which pharmacologic therapy may be directed for the prevention of lethal arrhythmias and sudden death. Finally, recent evidence suggests that transient acute ischemia may constitute an important triggering event for the development of lethal arrhythmias and sudden death in postinfarction patients.<sup>30,31</sup> The postinfarction dog model used in the present evaluation incorporates many of the etiologic features of sudden death and therefore may constitute a relevant model in which to assess pharmacologic agents for the prevention of sudden coronary death.

**Antiarrhythmic and antifibrillatory actions of dextro-rotatory sotalol.** In the present study, the administration of d-sotalol in a multiple-dose regimen (four 8 mg/kg intravenous doses over a 24-hour period) prevented the induction of VT by programmed ventricular stimulation in six of nine (67%) postinfarction dogs tested. This degree of efficacy against programmed stimulation-induced tachycardias is comparable to that reported for the single-dose acute administration of 8 mg/kg intravenous d-sotalol (54%)<sup>22</sup> and for the single-dose acute administration of racemic d,l-sotalol, 4.5 mg/kg intravenously (58%)<sup>18</sup> or 8.0 mg/kg intravenously (56%),<sup>19</sup> in similar postinfarction dog models. The selective increase in ventricular myocardial refractoriness in conjunction with the prolongation of paced QT and QT<sub>c</sub> intervals (general indices of action potential duration) suggest that the direct class III electrophysiologic actions of d-sotalol (i.e., a selective prolongation of action potential duration resulting in increased cellular refractoriness) may contribute to the antiarrhythmic actions of the isomer in the postinfarction dog model. In contrast, the unimpressive degree of beta-adrenergic receptor blockade produced by d-sotalol in this preparation, as well as the previously demonstrated lack of efficacy of the beta-adrenoceptor blockers metoprolol<sup>18</sup> and nadolol<sup>32</sup> against the induction of VT by programmed electrical stimulation in postinfarction dogs, argued against beta-adrenergic receptor blockade playing a role in the suppression of VT induction during programmed stimulation by the dextro-rotatory isomer of sotalol.

Administered in a multiple-dose pretreatment regimen (four 8 mg/kg intravenous doses over 24



hours), dextrorotatory sotalol provided significant protection against the development of ventricular fibrillation occurring in response to ischemia at a site distant from a previous infarction. The degree of protection afforded by this multiple-dose pretreatment was markedly greater than that afforded by a single-dose, acute pretreatment with 8 mg/kg intravenous d-sotalol in a previous investigation.<sup>22</sup> The enhanced efficacy of this multiple-dose regimen is presumably the result of optimization of drug plasma concentrations and/or cardiac tissue levels in the postinfarction dogs. Previous studies in this laboratory have identified the class III antiarrhythmic agents bretylium<sup>33</sup> and amiodarone,<sup>34</sup> the class III antiarrhythmic and beta-adrenoceptor-blocking agent d,l-sotalol,<sup>19</sup> and the beta-adrenergic receptor antagonist d,l-nadolol,<sup>32</sup> the latter apparently devoid of direct electrophysiologic actions, as providing significant protection against the development of ventricular fibrillation in response to ischemia at a site distant from a previous infarction. It may not be presumed, therefore, that the slight degree of beta-adrenoceptor blockade produced by d-sotalol in this preparation might not contribute to the antifibrillatory action of the isomer in the sudden death protocol. The slight degree of beta-adrenergic receptor blockade exhibited by d-sotalol in this regimen, however, does suggest that this agent may be tolerable in the setting of ventricular dysfunction.

During the present multiple-dose regimen, four of nine postinfarction dogs receiving dextrorotatory sotalol developed ventricular ectopic activity during or immediately after drug infusion. The development of ventricular premature complexes, with a comparable rate of occurrence and similar in characteristics of overdrive suppression, has been noted previously with the acute single-dose administration of the dextrorotatory but not the levorotatory isomer of sotalol.<sup>22</sup> In the present study, with small sample sizes, the development of transient ventricular ectopy upon d-sotalol administration did not correlate with the degree of QT interval prolongation. Further study will be required to determine the underlying mechanism of the d-sotalol-induced ventricular ectopy and to ascertain to what extent this adverse effect may limit the use of the agent.

**Conclusions.** In conscious dogs in the subacute phase of myocardial infarction, the dextrorotatory isomer of sotalol, administered in a multiple-dose, 24-hour treatment regimen, significantly suppressed the induction of VT by programmed ventricular stimulation and significantly protected against the development of ventricular fibrillation in response to ischemia at a site distant from a previous infarct.

Alterations in ventricular refractoriness, QT<sub>c</sub>, and paced QT intervals suggest that direct class III electrophysiologic actions (prolonged action potential duration, resulting in increased cellular refractoriness) might underlie, in part, the antiarrhythmic/antifibrillatory actions of d-sotalol in this preparation. The degree of beta-adrenergic receptor blockade produced by d-sotalol in this regimen was slight and unimpressive. These findings suggest the potential utility of d-sotalol in the prevention of VT and ventricular fibrillation in the setting of myocardial infarction.

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