The Effects of β-Adrenergic Stimulation on the Frequency-Dependent Electrophysiologic Actions of Amiodarone and Sematilide in Humans

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**Background** The autonomic nervous system appears to play an important role in the development of clinical ventricular arrhythmias, and β-adrenergic sympathetic stimulation may be important in modulating the electrophysiologic effects of class III antiarrhythmic agents. This study prospectively determined the effects of isoproterenol on the frequency-dependent actions of sematilide (a pure class III agent that selectively blocks the delayed rectifier potassium current) and amiodarone (a class III agent with a complex pharmacologic profile) on ventricular repolarization, refractoriness, and conduction.

**Methods and Results** The frequency-dependent electrophysiologic effects of sematilide (n=11) and amiodarone (n=22) were determined at (1) drug-free baseline, (2) during steady-state (>48 hours) dosing with sematilide (455±5 mg/d [mean±SEM]) or after 10.5 days of amiodarone loading (1618±32 mg/d), and (3) during isoproterenol administration (35 ng/kg per minute) to patients receiving sematilide or amiodarone. Electrophysiologic determinations were made at paced cycle lengths of 300 to 500 ms. The two groups were similar in all clinical characteristics. The ventricular action potential duration at 90% repolarization (APD90) was significantly prolonged by sematilide (mean increase, 7±1%; P<.01 by ANOVA) and amiodarone (mean increase, 12±1%; P<.001). However, while sematilide-induced APD90 prolongation was fully reversed to baseline values during isoproterenol infusion, the APD90 in patients receiving amiodarone remained significantly prolonged by a mean of 6±1% compared with baseline (P=.005). The reduction in the APD90 was frequency dependent for both agents, with a greater reduction at longer than shorter paced cycle lengths (P<.02). During isoproterenol infusion the right ventricular effective refractory period (RVERP) in patients receiving sematilide was significantly reduced to mean values of 8±2% below baseline (P<.05), whereas the RVERP in patients receiving amiodarone remained significantly prolonged by a mean of 7±1% above baseline values (P=.01). Sematilide and sematilide/amiodarone had no effect on ventricular conduction. Amiodarone increased the QRS duration by 14±6% (paced cycle length, 500 ms) to 32±5% (paced cycle length, 300 ms) compared with baseline values. Isoproterenol attenuated amiodarone-induced QRS prolongation by a mean of 5±1% (P=.005), without frequency-dependent effects, consistent with isoproterenol-induced increases in the sodium current. During isoproterenol infusion there was a trend for the sustained VT cycle length to be reduced below baseline in patients receiving sematilide (275±16 versus 298±55 ms, P=.06), whereas it remained significantly prolonged compared with baseline in patients receiving amiodarone (327±17 versus 257±12 ms, P<.001).

**Conclusions** Isoproterenol fully reversed the effects of selective potassium channel block with sematilide on the APD90 and further reduced the RVERP to values significantly below baseline; it partially attenuated but did not fully reverse amiodarone-induced prolongation of the APD90 and RVERP, which remained significantly prolonged beyond baseline values. Isoproterenol exerted frequency-dependent effects in both patient groups on the APD90; it modestly attenuated amiodarone-induced conduction slowing without frequency-dependent actions; and the sustained VT cycle length remained significantly prolonged during isoproterenol administration to patients receiving amiodarone but not in those receiving sematilide. These findings may have important clinical implications regarding protection from arrhythmia development in patients receiving pure class III agents or amiodarone. (*Circulation. 1994;90:1811-1819.*)

**Key Words** • amiodarone • sematilide • action potential duration • isoproterenol

The negative results of the Cardiac Arrhythmia Suppression Trial using class I antiarrhythmic agents1-3 and the high efficacy of amiodarone in patients with sustained ventricular arrhythmias4-6 have resulted in a major investigative effort in controlling ventricular arrhythmias by lengthening ventricular repolarization. A large number of selective class III agents (eg, sematilide,5-8 dofetilide,9 E-4031,10 and d-sotalol11) whose sole electrophysiologic action is to lengthen the ventricular action potential duration (APD) have been developed. Sematilide hydrochloride is a methysulfonfonyl-amino parasubstituted analogue of procainamide that selectively blocks the delayed rectifier potassium current (Ik)5-8 without other pharmacological effects in animals or humans.5-8

β-Adrenergic sympathetic activity has been implicated as a provoker of malignant ventricular arrhythmias,12-14 and catecholamine administration has been
shown to facilitate the induction of ventricular arrhythmias during programmed stimulation in patients without inducible ventricular tachycardia (VT) in the baseline drug-free state. Therefore, it has been demonstrated that β-adrenergic catecholamine administration can reverse the electrophysiologic effects of various class I antiarrhythmic agents and facilitate the induction of ventricular arrhythmias during electrophysiologic study in patients receiving these medications. This may explain in part the recurrence of clinical ventricular arrhythmias despite predicted efficacy during electrophysiologic testing in patients receiving these medications.

β-Adrenergic catecholamines may modulate antiarrhythmic drug action by stimulating a number of currents in ventricular cells, including the inward sodium current (I\textsubscript{Na}), delayed rectifier potassium current (I\textsubscript{K}), the Na-K pump current, the transient outward potassium current (I\textsubscript{to}), the chloride current, the slow inward calcium current, and the pacemaker current (I\textsubscript{f}). The overall effect in humans is for the ventricular APD and refractory period to shorten. Isoproterenol fully reversed E-4031–induced prolongation of the refractory period in isolated guinea pig ventricular myocytes, but no studies in humans have examined the effects of β-adrenergic catecholamines on the electrophysiologic effects of pure class III agents. Modulation of the electrophysiologic actions of these agents by β-adrenergic catecholamines may have important ramifications regarding the clinical use of these agents. In addition, amiodarone has antiadrenergic actions that may render it less susceptible to reversal during catecholamine administration. One previous study has shown that epinephrine partially attenuates amiodarone-induced increases in the ventricular effective refractory period, but no studies have examined the effects of β-adrenergic catecholamines on amiodarone-induced prolongation of the APD, ventricular conduction, or modulation of the agent’s frequency-dependent actions. These are important issues because amiodarone exerts its clinical actions in part by slowing conduction and lengthening refractoriness by both voltage-dependent (secondary to APD prolongation) and time-dependent (independent of APD) processes.

The purpose of this study was to determine the effects of isoproterenol on the frequency-dependent actions of sematilide and amiodarone on ventricular repolarization, refractoriness, and conduction.

### Methods

#### Patient Population

Patients were eligible for this prospective study if they had (1) clinical sustained VT, ventricular fibrillation, aborted sudden cardiac death, or syncope resulting from VT, (2) inducible sustained VT during baseline drug-free electrophysiologic study, and (3) they were treated for clinical indications with either sematilide or amiodarone. Exclusion criteria included myocardial infarction within the last 2 months, greater than class II angina, and ongoing therapy with β-blockers or calcium channel blockers. All patients were chemically euthyroid.

### Study Protocol

Patients underwent electrophysiologic study in the baseline drug-free state and were treated with either sematilide or amiodarone, as dictated by the patient’s clinical scenario. Sematilide was initiated as previously described at 100 mg PO q 8 hours and increased to 125 to 150 mg PO q 8 hours. Electrophysiologic study was performed at steady state (> 48 hours, since the elimination half-life is approximately 8 hours). Patients receiving amiodarone were loaded with 800 mg PO q 12 hours, and electrophysiologic study was repeated after approximately 10 days of oral therapy. After the electrophysiologic determinations were made in patients receiving sematilide or amiodarone, electrophysiologic measurements were repeated during continuous isoproterenol (35 ng/kg per minute) infusion after a 12-minute equilibration period. This dose of isoproterenol has been shown to result in an approximately 25% to 30% increase in the heart rate of patients not receiving antiarrhythmic therapy and thus approximates the heart rate changes associated with moderate exercise.

#### Electrophysiologic Study

Electrophysiologic study was performed in the baseline drug-free state after discontinuation of β-blockers, antiarrhythmic agents, and calcium channel blockers for ≥6 half-lives. Electropharmacological testing was performed 6 to 8 hours after the last dose of sematilide or amiodarone. A 7F catheter with a silver-silver chloride distal electrode pair was placed at the right ventricular (RV) apex and used to record the monophasic action potential duration (EP Technology). The catheter has a second pair of platinum ring electrodes located 2 mm from the catheter tip that were used for pacing, thus permitting the determination of ventricular repolarization and refractoriness at the same ventricular site.

#### Pacing Protocol

The electrophysiologic measurements were performed at (1) drug-free baseline, (2) during drug therapy, and (3) during concomitant drug therapy and isoproterenol. Ventricular pacing was performed at a pulse width of 2 ms at twice diastolic threshold. Monophasic action potential (MAP) recordings were determined at paced cycle lengths of 300, 350, 400, and 500 ms for 150 to 200 beats. The catheter position was recorded during the baseline electrophysiologic study and placed in a similar position during the subsequent electropharmacologic study. The MAP was recorded at a paper speed of 100 to 150 mm/s (MIDAS, PPG Industry). MAP amplitude was determined from the diastolic baseline to the plateau, and the APD\textsubscript{50} was measured from the beginning of phase 0 until repolarization was 90% complete. Only MAP recordings ≥8 μV were used. Three APD complexes were measured at each paced cycle length by one blinded observer. Intraobserver variability was <5%.

The RV effective refractory period (RVERP) was measured at the same site from which the MAP recordings were obtained. An extrastimulus was applied during late diastole after a 14-beat drive run and a 1-second pause between drive runs. The coupling interval of the extrastimulus was successively decremented by 5 ms, and the effective refractory period was reached when the extrastimulus failed to provoke an extrasystole on two successive attempts.

The QRS duration was used as a measure of ventricular conduction and was determined during steady-state ventricular pacing by measuring from the beginning to the end of the QRS complex in ECG lead II. One blinded observer measured two QRS complexes at each paced cycle length. The intraobserver variability was <5%.

After the above determinations were made in patients receiving sematilide or amiodarone, attempts were made to induce sustained monomorphic VT using programmed ventricular stimulation at the RV apex and RV outflow tract using ≤3 premature extrastimuli as previously described. VT was
considered sustained if it lasted ≥30 seconds or required premature termination because of hemodynamic compromise. If a hemodynamically stable sustained VT was induced during the electropharmacological study, attempts were made to reinstate the same morphologic ventricular tachycardia during isoproterenol administration. No attempt was made to induce sustained VT during isoproterenol infusion if VT was not induced during pharmacological therapy alone.

**Data Analysis**

The Fisher's exact test was used to analyze categorical data and the Student's paired t test (two tailed) for means of clinical data. The means of electrophysiological or hemodynamic data, the changes in the APD₉₀, RVERP, QRS duration, and RVERP/APD₉₀ during drug therapy and isoproterenol administration, and the consistency of these changes compared with drug therapy or baseline as a function of the paced cycle length were determined using repeated-measures ANOVA with the Greenhouse-Geisser⁴¹ correction for within-subject correlations. Data are expressed as mean±SEM. Significance was defined as a probability level of ≤0.05.

**Results**

**Patient Population**

There were 11 patients in the sematilide group and 22 patients in the amiodarone group. The mean dose of sematilide was 455±5 mg/d and of amiodarone was 1618±32 mg/d administered over a mean of 10.5±.5 days before electropharmacological testing. There were no differences in age, history of clinical arrhythmias, left ventricular ejection fraction, or left ventricular dimensions in the two study groups. (See Table.)

**Sinus Cycle Length and Blood Pressure**

The sinus cycle length was not altered by sematilide administration (843±57 to 811±39 ms, P=NS) but with the addition of isoproterenol was significantly reduced to 545±36 ms (33% decrease from sematilide alone; P<.001 versus sematilide or baseline by repeated-measures ANOVA). During amiodarone therapy the sinus cycle length increased from 768±26 to 871±33 ms (P=.01) and decreased to 625±30 ms during isoproterenol infusion in patients receiving amiodarone (28% decrease versus amiodarone alone; P<.001 versus amiodarone or baseline). The reduction in the sinus cycle length during isoproterenol infusion compared with drug therapy alone was similar in patients receiving sematilide or amiodarone (266±51 versus 246±31 ms; P=NS).

The administration of isoproterenol to patients receiving sematilide or amiodarone did not significantly alter systolic blood pressure (sematilide: 119±9 versus 121±10 mm Hg, P=NS; amiodarone: 124±5 versus 116±4 mm Hg, P=NS) or diastolic blood pressure (sematilide: 74±6 versus 73±3 mm Hg, P=NS; amiodarone: 74±3 versus 69±3 mm Hg, P=NS).

**Effect on Repolarization**

After sematilide administration (Fig 1), the APD₉₀ was significantly increased by 10±4 ms (5%), 14±5 ms (6%), 14±5 ms (6%), and 24±7 ms (10%) above baseline values at paced cycle lengths of 300, 350, 400, and 500 ms, respectively (P=.01 by ANOVA). There was a trend (P=.07 by ANOVA) over the paced cycle lengths examined for sematilide to prolong the APD₉₀ to a greater extent at longer than at shorter paced cycle lengths (i.e., “reverse” frequency-dependence). During isoproterenol infusion, the sematilide-induced prolongation of the APD₉₀ was reduced by 12±4 ms (6%), 19±4 ms (8%), 24±4 ms (10%), and 34±9 ms (12%) at paced cycle lengths of 300, 350, 400, and 500 ms (P<.001). Thus, sematilide-induced increases in the APD₉₀ were fully reversed, and there was a nonsignificant trend for the values to be reduced by 1±2% to 5±2% below baseline values (P=NS). Isoproterenol exerted significant frequency-dependent actions on the APD₉₀ in patients receiving sematilide. The reduction in the APD₉₀ during isoproterenol infusion was more

**Clinical Characteristics**

<table>
<thead>
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<th>Drug dose, mg/d</th>
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<td>63±2</td>
<td>NS</td>
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<td>66%</td>
<td>NS</td>
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<tr>
<td>LVEDD, mm</td>
<td>62±3</td>
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SUS VT/VF indicates sustained ventricular tachycardia/ventricular fibrillation; MI, myocardial infarction; CHF, congestive heart failure; LVESD, left ventricular end-systolic dimension; and LVEDD, left ventricular end-diastolic dimension.

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**Fig 1.** Graphs show frequency-dependent effects on the APD₉₀. Left, Sematilide and sematilide plus isoproterenol. Right, Amiodarone and amiodarone plus isoproterenol. Sematilide-induced APD₉₀ prolongation was fully reversed by isoproterenol, whereas amiodarone's effects on the APD₉₀ were attenuated with isoproterenol but remained significantly prolonged compared with baseline values (P=.005).
marked at longer than at shorter paced cycle lengths (P<.02).

Amiodarone significantly prolonged the APD₉₀ (Fig 1) by 26±5 ms (13%), 28±5 ms (13%), 31±4 ms (13%), and 27±4 ms (11%) at paced cycle lengths of 300, 350, 400, and 500 ms, respectively (P<.0001 by ANOVA) without frequency-dependent effects. During isoproterenol administration to patients receiving amiodarone, the APD₉₀ was reduced by 13±3 ms (5%), 20±4 ms (7%), 18±3 ms (7%), and 21±4 ms (7%) at paced cycle lengths of 300, 350, 400, and 500 ms, respectively (P<.001). In contrast to sematilide, amiodarone-induced APD₉₀ prolongation was attenuated but not reversed during isoproterenol administration, and the APD₉₀ during isoproterenol remained significantly prolonged by 4±2% to 8±2% compared with baseline values (P=.005). Similar to patients receiving sematilide, the reduction in the APD₉₀ during isoproterenol infusion was greater at longer than at shorter paced cycle lengths (P<.02). There were no frequency-dependent effects between baseline and amiodarone/isoproterenol.

**Effects on Refractoriness**

During sematilide administration the RVERP (Fig 2) was increased from baseline by 15±9 ms (8%), 21±8 ms (11%), 23±8 ms (11%), and 28±8 ms (12%) at paced cycle lengths of 300, 350, 400, and 500 ms (P=.02 by ANOVA). Sematilide-induced APD₉₀ prolongation was greater at longer than at shorter paced cycle lengths (P=.05). During isoproterenol administration, the RVERP in patients receiving sematilide was reduced by 31±5 ms (14%), 36±3 ms (16%), 36±5 ms (15%), and 36±9 ms (16%) to values significantly below baseline (P<.05). In patients receiving sematilide, the reductions below baseline values were 21±9 ms (10%), 19±9 ms (9%), 19±8 ms (8%), and 11±8 ms (4%) at paced cycle lengths of 300, 350, 400, and 500 ms, respectively (P<.05). Isoproterenol-induced changes in the RVERP in patients receiving sematilide were not frequency dependent.

During amiodarone therapy, the RVERP (Fig 2) was increased by 34±4 ms (17%), 37±5 ms (18%), 38±5 ms (17%), and 43±6 ms (19%) at paced cycle lengths of 300, 350, 400, and 500 ms without significant frequency-dependent effects. Similar to the results evaluating the APD₉₀, isoproterenol administration attenuated but did not reverse amiodarone-induced RVERP prolongation. During isoproterenol administration the RVERP was reduced by 23±5 ms (9%), 27±6 ms (10%), 28±5 ms (10%), and 26±5 ms (9%) at paced cycle lengths of 300, 350, 400, and 500 ms, respectively (P<.001). However, the RVERP remained significantly prolonged above baseline values by 12±3 ms (7%), 14±3 ms (7%), 12±3 ms (6%), and 17±3 ms (8%) at paced cycle lengths of 300, 350, 400, and 500 ms, respectively (P=.01). Isoproterenol’s effects on the RVERP were not frequency dependent.

**Effects on Conduction**

Sematilide alone (Fig 3) and after isoproterenol did not effect ventricular conduction as determined by the QRS duration. Amiodarone (Fig 3) increased the QRS duration in a frequency-dependent manner with significantly greater prolongation at longer than at shorter
paced cycle lengths \((P<.001\) by ANOVA). The QRS duration was increased from baseline by 23±6 ms (14%) at a paced cycle length of 500 ms and by 52±8 ms (32%) at a paced cycle length of 300 ms \((P<.001)\). During isoproterenol administration in patients receiving amiodarone, the QRS duration was reduced by 8±4 ms (4%), 10±4 ms (5%), 8±4 ms (5%), and 10±3 ms (6%) at paced cycle lengths of 300, 350, 400, and 500 ms, respectively \((P=.005)\), indicating isoproterenol-induced facilitation of ventricular conduction. Isoproterenol did not alter the frequency-dependent relation of amiodarone on ventricular conduction compared with baseline.

**RVERP/APD\(_{90}\) Ratio**

The baseline RVERP/APD\(_{90}\) ratio was increased at shorter paced cycle lengths in both patient groups \((P<.01\) by ANOVA). Sematilide (Fig 4) had no effect on the RVERP/APD\(_{90}\) ratio compared with baseline. However, during isoproterenol administration, the ratio was significantly reduced compared with sematilide alone \((P<.04\) versus sematilide), consistent with a greater reduction in the RVERP than the APD\(_{90}\) by isoproterenol, particularly at shorter cycle lengths.

Amiodarone (Fig 4) significantly increased the RVERP/APD\(_{90}\) ratio compared with baseline \((P=.04)\), consistent with greater prolongation of refractoriness than repolarization. Isoproterenol had no significant effect on this ratio \((P=NS\) versus baseline or amiodarone alone).

**Ventricular Tachycardia Cycle Length**

In the sematilide group, sustained monomorphic VT was induced in 10 patients and sustained polymorphic VT in 1 patient in the drug-free state. After sematilide administration, sustained monomorphic VT was induced in 7 patients, and 4 patients had no inducible sustained VT. When morphologically similar monomorphic VTs were compared, there was a nonsignificant increase in the VT cycle length during sematilide therapy compared with baseline (Fig 5) but a significant decrease in the VT cycle length during isoproterenol administration compared with patients receiving sematilide \((n=6; 317±19\) versus 275±15 ms; \(P=.006)\). In addition, there was a trend for the VT cycle length to be decreased below baseline \((n=6; 275±15\) versus 298±55 ms; \(P=.06)\) during sematilide and isoproterenol. The reduction in VT cycle length during isoproterenol to patients receiving sematilide was significantly correlated to the reduction in RVERP \((r=.95, P=.014)\) but not to changes in the APD\(_{90}\) \((r=.68, P=NS)\) or QRS duration \((r=.52, P=NS)\). In the amiodarone group, sustained monomorphic VT was induced in 17 patients and sustained polymorphic VT in 5 patients during drug-free baseline electrophysiologic study. After amiodarone administration, sustained monomorphic VT was inducible in 16 patients, sustained polymorphic VT was inducible in 2 patients, and 4 patients had no inducible sustained VT. Amiodarone significantly prolonged the cycle length of morphologically similar monomorphic ventricular tachycardias compared with baseline values.

**Fig 4.** Graphs show frequency-dependent effects on the ratio of the right ventricular effective refractory period and the action potential duration at 90% repolarization (RVERP/APD\(_{90}\)). Left, Sematilide and sematilide plus isoproterenol. Right, Amiodarone and amiodarone plus isoproterenol. During isoproterenol administration to patients receiving sematilide, the RVERP/APD\(_{90}\) ratio was significantly reduced \((P=.02)\). Amiodarone significantly increased the RVERP/APD\(_{90}\) compared with baseline values \((P<.04)\), and isoproterenol had no significant effect on the RVERP/APD\(_{90}\).

**Fig 5.** Graphs show effect on sustained monomorphic ventricular tachycardia (VT) cycle length. Top, Baseline, sematilide, and sematilide plus isoproterenol. Bottom, Baseline, amiodarone, and amiodarone plus isoproterenol. During isoproterenol administration to patients receiving sematilide, the sustained VT (SUS VT) cycle length was significantly reduced \((P=.006)\) compared with sematilide alone and nonsignificantly reduced \((P=.06)\) compared with baseline drug-free values. Whereas isoproterenol administration to patients receiving amiodarone significantly reduced \((P=.015)\) the sustained VT cycle length, the sustained VT cycle length remained significantly prolonged \((P<.001)\) compared with baseline drug-free values.
(Fig 5), and the VT cycle length was significantly decreased during isoproterenol administration (n=14; 363±19 to 329±19 ms, P=.015) compared with amiodarone alone. In contrast to sematilide, the VT cycle length of patients receiving amiodarone and isoproterenol remained significantly prolonged compared with baseline drug-free values (327±17 versus 257±12 ms, P<.001). The reduction in VT cycle length during isoproterenol in patients receiving amiodarone was not significantly correlated to reductions in RVERP (r=.18, P=NS), APD90 (r=.38, P=NS), or QRS duration (r=.23, P=NS).

Discussion

We have previously described the individual frequency-dependent actions of amiodarone and sematilide.5 This is the first study to examine the effects of β-adrenergic catecholamines on the electrophysiologic effects of a pure class III agent and on the frequency-dependent effects of amiodarone. The new findings of this study are that (1) isoproterenol administration fully reversed the effects of sematilide on the APD90 and further reduced the RVERP to values significantly below baseline determinations; (2) isoproterenol partially attenuated but did not fully reverse amiodarone-induced prolongation of the APD90 and RVERP, which remained significantly prolonged from baseline values; (3) isoproterenol exerted frequency-dependent effects in both patient groups on the APD90, with a greater reduction in the APD90 at longer than at shorter paced cycle lengths; (4) isoproterenol modestly attenuated amiodarone-induced conduction slowing without frequency-dependent effects; and (5) the sustained VT cycle length remained significantly prolonged during isoproterenol administration to patients receiving amiodarone but not in patients receiving sematilide.

Effects on Conduction

Sematilide, as previously described,5 had no effect on ventricular conduction, and isoproterenol did not modify the QRS duration. Amiodarone's frequency-dependent slowing of ventricular conduction is consistent with the drug's known ability to decrease Vmax by blocking Na channels and slowing their recovery during the interpulse interval.36,37 The observed partial reversal of amiodarone's effects on conduction are consistent with the finding that isoproterenol increases the inward sodium current (I\textsubscript{Na}) in rabbit cardiac myocytes23,24 and guinea pig myocytes,26 although this has not been a universal finding in isolated cells.42,43 Most pertinent to the current study, Lee et al24 have recently shown that isoproterenol antagonizes lidocaine-induced sodium channel block in isolated rabbit cardiac myocytes and attenuates but does not fully reverse lidocaine-induced conduction slowing in isolated rabbit hearts. Epstein et al44 have demonstrated that isoproterenol (approximately 150 ng/kg per minute) reversed amiodarone-induced increases in His-Purkinje conduction time in canines. We have extended these findings to humans by demonstrating that isoproterenol partially reversed amiodarone-induced slowing of ventricular conduction and that this attenuation of conduction slowing is not frequency dependent. The QRS duration was reduced by a fixed amount of 4% to 6% at each paced cycle length. Thus, isoproterenol may increase I\textsubscript{Na} without altering the steady-state kinetics of Na channel activation or inactivation by amiodarone. This is consistent with the finding in isolated rabbit myocytes that isoproterenol increases I\textsubscript{Na} without altering the kinetics of sodium channel blockade or recovery by lidocaine (which has similar Na channel-blocking kinetics as amiodarone).24 In addition to possible direct effects on the inward sodium current, isoproterenol may improve conduction during amiodarone administration (1) by decreasing the APD90 with subsequent increases in the interpulse interval, allowing a longer time period for Na channel recovery and subsequent facilitation of ventricular conduction; (2) by shortening the plateau, whereby there may be less amiodarone binding to Na channels and less amiodarone-induced reduction in I\textsubscript{Na}; (3) by causing hyperpolarization of the cell with subsequent reduction in amiodarone-induced Na blockade; and (4) possibly by facilitating conduction across gap junctions or improving cell-to-cell coupling.46

Effects on Repolarization and Refractoriness

This study demonstrates that a dose of isoproterenol that results in physiological changes in heart rate in the drug-free state consistent with moderate physical exercise caused sematilide-induced APD90 prolongation to be fully reversed. Isoproterenol activates a variety of ventricular myocyte currents including the delayed rectifier potassium current (I\textsubscript{K}), the Na-K pump current, the transient outward potassium current (I\textsubscript{O}), the chloride current (I\textsubscript{Cl}), and the slow inward calcium current (I\textsubscript{Ca}).23,34 Although the effect of isoproterenol on isolated myocytes can be an increase or decrease in the APD90 based on the relative activation of different currents (eg, increases in I\textsubscript{K} or the Na-K pump current shorten the APD90, whereas increases in I\textsubscript{Ca} prolong repolarization), we observed a consistent decrease in sematilide and amiodarone-induced APD90 prolongation. The specific mechanism by which isoproterenol reverses sematilide’s effect on the APD90 is beyond the scope of this study. However, in isolated guinea pig myocytes, E-4031 (a specific blocker of the rapidly activating component of the delayed rectifier potassium current [I\textsubscript{K1}])—induced prolongation of the RVERP and APD90 is reversed by isoproterenol secondary to isolated increases in I\textsubscript{K1} (the slowly activating component of the delayed rectifier) and the chloride current.10 The relative effects of sematilide on I\textsubscript{K1} and I\textsubscript{Ca} have not been defined, but it seems likely, based on the known effects of isoproterenol, that isoproterenol reverses sematilide’s effects by increasing one or more components of the delayed rectifier (I\textsubscript{K}) along with the chloride current.

When the RVERP/APD90 ratio is examined at baseline or after sematilide alone, the ratio increased at shorter cycle lengths compared with longer cycle lengths (P<.01), consistent with lengthening of the RVERP relative to the APD90. This most likely reflects the lack of full recovery of sodium channels during the interpulse interval with a mild subsequent prolongation of the RVERP relative to the APD90 (ie, time-dependent refractoriness).36,37,47 This phenomenon was not observed during isoproterenol in patients receiving sematilide. The significant reduction in the RVERP/APD90 ratio during isoproterenol infusion compared with sematilide alone is consistent with the RVERP being
more sensitive to isoproterenol than is the APD90. Overall, the RVERP was reduced by an additional 21±4 ms (P=.007) compared with the APD90 during isoproterenol administration to patients receiving sematilide. Possible explanations for the lack of postrepolarization refractoriness during rapid pacing and isoproterenol infusion include (1) isoproterenol-induced increases in the inward sodium current23 at each depolarization negating the RVERP prolonging effects of a lack of full recovery of Na channels at the end of repolarization, (2) shortening of the plateau with subsequent enhanced recovery of sodium channels, (3) hyperpolarization of myocardial cells with more sodium channels available at a fixed diastolic interval,25 and (4) possibly an increase in the space constant by sematilide enhancing the effects on the RVERP of any increase in INa by isoproterenol.48

In contrast to the results obtained with selective delayed rectifier (IKr) block by sematilide, amiodarone-induced prolongation of the APD90 and RVERP was attenuated during isoproterenol but still remained significantly prolonged beyond baseline. Thus, even during moderate β-adrenergic stimulation, amiodarone still exerted significant pharmacological effects. During isoproterenol, the sinus cycle length was reduced to values below baseline, and the reduction in sinus cycle length was similar to that observed during sematilide, whereas the alterations in repolarization and refractoriness in the amiodarone group were considerably less marked. Although the difference in the response to β-adrenergic catecholamines during amiodarone at the sinus node and in the ventricle may be explained by different sensitivities of sinus nodal and ventricular tissue to β-adrenergic catecholamines, it raises the possibility that amiodarone’s relative protection from reversal of repolarization and refractoriness during isoproterenol may not be solely secondary to its antiadrenergic actions but might also be related to direct effects on ionic currents, such as nonselective block of IKs.

It is interesting that there was a more marked reduction in the APD90 in both patient groups by isoproterenol at longer than at shorter paced cycle lengths. Jurkiewicz and Sanguinetti26 have shown that during rapid pacing, there is incomplete deactivation of the slowly activating component of the delayed rectifier (IKs) in myocytes exposed to dofetilide (a selective IKs blocker), and Sanguinetti et al10 have demonstrated that isoproterenol reverses APD90 prolongation by E-4031 by increasing IKs and the chloride current. Thus, if isoproterenol-induced attenuation of ami dolarone’s or sematilide’s effect on repolarization is, in part, by increasing IKs, these effects may be less pronounced at shorter cycle lengths because rapid pacing has already resulted in significant increases in IKs. Subsequently, there is less contribution by isoproterenol to outward repolarizing K currents at short paced cycle lengths. Another possibility is that isoproterenol-induced potassium translocation into cells may decrease the normal accumulation of potassium between cells during rapid pacing, which has been shown to increase outward potassium currents and enhance repolarization at short cycle lengths.59,51

Previous Studies
Our results are consistent with those of Calkins et al,22 who examined the reversal of amiodarone-induced prolongation of the RVERP during epinephrine infusion and observed a 20% to 36% relative reduction in amiodarone-induced RVERP prolongation (frequency-dependent effects and conduction were not measured). The somewhat larger reductions in the RVERP in our study along with the mild decrease in the VT cycle length during isoproterenol in patients receiving amiodarone is probably related to the more potent β-adrenergic stimulation in the current investigation. Calkins et al22 used epinephrine, which, on a weight basis, is not as potent a stimulator of cardiac β-receptors as is isoproterenol. They only observed a reduction in the sinus cycle length of 4.5% to 7.7% during epinephrine administration in patients receiving amiodarone compared with 28% observed in the current study. In addition, epinephrine stimulates α-receptors, which lengthens the RVERP and may attenuate the effects of β-stimulation on refractoriness.52 Brugada et al53 reported a significant reduction in antegrade accessory pathway effective refractory period during isoproterenol infusion in patients receiving low-dose (200 mg/d) amiodarone therapy. Since the baseline accessory pathway ERP was not determined, it is difficult to assess whether amiodarone’s effects were fully reversed or simply attenuated. In addition, the amiodarone dose used in the current study was considerably higher and amiodarone’s sensitivity to reversal may be dose related.

Clinical Implications
This is the first study in humans to examine the potential for pure class III agents to have their electrophysiologic actions reversed by β-adrenergic catecholamines, and the findings may have important clinical implications. The full reversal of all of sematilide’s electrophysiological effects to values at or below baseline during isoproterenol administration suggests that the antiarrhythmic actions of sematilide, and possibly compounds with a similar electrophysiologic profile, may be readily reversed during daily physical activities. This could potentially leave patients without arrhythmic protection for variable periods of time and may account for some episodes of arrhythmic recurrence despite favorable results during electropharmacological testing. Indeed, we have previously reported that two of three arrhythmic recurrences that we have observed during sematilide therapy occurred during high catecholaminergic states.5 Our findings raise the question of whether pure class III agents should be administered in conjunction with β-blockers, although there is a concern that bradycardia might increase the risk of torsade de pointes. While this can only be answered by a clinical trial, preliminary data do not appear to indicate that d,l-sotalol has a higher incidence of torsade than either d-sotalol or sematilide,54,55 and amiodarone, which slows the heart rate and lengthens the APD90, has an unusually low incidence of torsade de pointes. In addition, d,l-sotalol–induced increases in the APD90 and RVERP are not attenuated during isoproterenol administration (similar dosing as used in this study), presumably due to the β-blocker properties of this compound.56 In contrast to the findings with sematilide, the continued maintenance of electrophysiologic effects of amiodarone during isoproterenol suggests that the high efficacy of this agent may be due in part to its continued antiarrhythmic effects during β-adrenergic stimulation. In addition to
maintained prolongation of the ventricular RVERP, APD₀₉₀, and conduction by amiodarone, the reduction in the VT cycle length during isoproterenol administration was only modest (mean, 34 ms), and the VT cycle length remained significantly prolonged above baseline values, suggesting that β-adrenergic stimulation in patients receiving amiodarone is not likely to make a hemodynamically stable arrhythmia unstable by markedly decreasing the VT cycle length.

Limitations

Only a relatively narrow range of cycle lengths (300 to 500 ms) could be tested because of sinus interference at longer cycle lengths and hemodynamic effects at shorter paced cycle lengths. Effects on ventricular conduction were inferred by measuring the QRS duration because it correlates closely with changes in V max in vitro.56 Because of time considerations, it was not possible to administer an intravenous β-blocker during isoproterenol infusion to determine if β-blockade would reverse all of the electrophysiological effects of isoproterenol. The effects of sematilide, amiodarone, or isoproterenol on the electrophysiological parameters of cells comprising the arrhythmic circuit may be different from those at the RV recording site.

Conclusions

The effects of pure I K block with sematilide on the APD₀₉₀ and RVERP are reduced to values at or significantly below baseline during isoproterenol administration, whereas amiodarone’s effects on the APD₀₉₀, RVERP, ventricular conduction, and VT cycle length are attenuated but remain significantly prolonged beyond baseline during isoproterenol infusion. These findings may have important clinical implications regarding protection from arrhythmia development in patients receiving pure class III agents or amiodarone.

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