Differential Effects of Isoproterenol on Sustained Ventricular Tachycardia Before and During Procainamide and Quinidine Antiarrhythmic Drug Therapy

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Background. Autonomic modulation, especially increased sympathetic activity, may play a role in the genesis of ventricular arrhythmias. The purpose of this study was to determine whether β-sympathetic stimulation with isoproterenol would alter sustained ventricular tachycardia (VT) circuits similarly during the drug-free and antiarrhythmic drug-treated states.

Methods and Results. Twenty-five patients with repeatedly inducible, hemodynamically stable, sustained VT were evaluated by programmed ventricular stimulation. In the antiarrhythmic drug-free state, isoproterenol (0.03 μg/kg per minute) shortened the following intervals (in milliseconds; mean±SEM; 25 patients; paired t test): sinus cycle length (792±37 to 568±18; p<0.001), ventricular paced QT interval (386±8 to 348±6; p<0.001), ventricular paced QRS duration (185±4 to 182±4; p=0.014), ventricular effective (238±5 to 208±4; p<0.001) and functional (261±6 to 227±5; p<0.001) refractory periods, and the VT cycle length (VTCL) (311±9 to 291±9; p<0.001). Isoproterenol (0.03 μg/kg per minute) was administered during 31 antiarrhythmic drug trials (procainamide, n=18; quinidine, n=13) in 22 patients. Isoproterenol shortened the sinus cycle length, QT interval during ventricular pacing, and ventricular effective and functional refractory periods before and during procainamide and quinidine therapy (ANOVA; isoproterenol effect, p≤0.0002 for all). The amount of decrease in these intervals with isoproterenol was the same before and during procainamide and quinidine therapy (ANOVA interaction, p=NS for all). The QRS duration during ventricular pacing and VTCL were also shortened by isoproterenol before and during procainamide (baseline, n=17; QRS, 182±4 to 178±4 msec; VTCL, n=18, 314±11 to 291±11 msec; during procainamide, QRS, 218±7 to 197±6 msec; VTCL, 422±15 to 359±11 msec) and quinidine (baseline, n=13; QRS, 190±6 to 185±5 msec; VTCL, n=12, 298±10 to 280±9 msec; during quinidine, QRS, 223±9 to 208±8 msec; VTCL, 415±14 to 355±10 msec) (isoproterenol effect p<0.0003 for all). However, the amount of decrease in QRS duration and VTCL with isoproterenol was greater during procainamide and quinidine than in the drug-free state (ANOVA interaction, p≤0.02 for all). These changes continued to be significant when normalized for the initial QRS duration and VTCL (p<0.03 for all).

Conclusions. Isoproterenol affects presumed reentrant sustained VT circuits less in the absence of antiarrhythmic drugs but markedly attenuates the antiarrhythmic drug-induced slowing of sustained VT. To the extent that the change in QRS duration reflects a change in conduction within the VT circuit, these results imply that the attenuation of drug-induced slowing of VT by isoproterenol is due to a greater change in conduction rather than refractoriness. (Circulation 1993;87:783–792)

Key Words • isoproterenol • tachycardia, ventricular • procainamide • quinidine

Autonomic modulation, especially increased sympathetic activity, may play an important role in the genesis of ventricular arrhythmias. The β-agonist isoproterenol has been used to induce ventricular arrhythmias that occur with exercise.1-4 Isoproterenol can also facilitate the induction of ventricular tachy-
duction,\textsuperscript{11} creating the proper substrate for reentry to occur.

The effect of isoproterenol on inducible sustained VT, where the substrate for reentry is presumably already present, is unknown in humans. By administering isoproterenol to patients with inducible VT before and during antiarrhythmic therapy, insights into the mechanism of its drug effect(s) on VT circuits and clinically relevant information regarding the ease of VT induction and hemodynamic stability during VT might be obtained. Our preliminary study in a small number of patients using a variety of antiarrhythmic drugs demonstrated some effect of isoproterenol on sustained VT.\textsuperscript{12} The purpose of our study was to 1) investigate whether $\beta$-adrenergic stimulation (isoproterenol infusion) affected induced sustained VT before and during procainamide and quinidine antiarrhythmic therapy and 2) attempt to delineate the mechanism by which the changes occur.

**Methods**

**Patient Population**

Twenty-five patients underwent programmed ventricular stimulation in the fasting, nonsedated state after giving informed oral and written consent. Patients were included in the study if sustained (>30-second duration) hemodynamically stable VT could be induced reproducibly at electrophysiological study. Patients with recent myocardial infarction (<3 months before study) or unstable angina were excluded. For the drug-free tests, all antiarrhythmic drugs were discontinued at least five half-lives before electrophysiological testing. No patient was previously treated with amiodarone, and no patient was receiving a $\beta$-blocker during the initial or subsequent studies.

**Electrophysiological Study**

At the time of the initial study, two or more multipolar electrode catheters were inserted percutaneously into a femoral vein and advanced under fluoroscopic guidance to the right ventricular apex and across the tricuspid valve in the area of the His bundle. Programmed ventricular stimulation was performed with ventricular stimuli of 2-msec duration at twice late diastolic threshold with a custom-built programmable stimulator. Bipolar intracardiac recordings filtered at 30–500 Hz and three or more standard ECG leads filtered at 0.1–25 Hz were displayed simultaneously on a multichannel oscilloscope and recorded at paper speeds of 50–150 mm/sec.

An escalating ventricular stimulation protocol was used until sustained VT was induced reproducibly.\textsuperscript{13} In brief, progressively premature single ($S_i$) and double ($SS_i$) ventricular stimuli were introduced after eight complexes of sinus rhythm and then during ventricular pacing ($S_v$) at multiple pacing cycle lengths (600, 500, and 400 msec) at the right ventricular apex. If VT was not induced, the protocol was repeated at a second ventricular site. If VT was still not induced, a third ventricular extrastimulus ($S_x$) was introduced at both sites. In two patients in whom the spontaneously occurring VT morphology was known (12-lead ECG), a fourth ventricular extrastimulus ($S_x$) was used to induce reproducibly a VT morphology identical to the spontaneously occurring VT. The entire programmed ventricular stimulation protocol was then repeated beginning 10 minutes after the initiation of isoproterenol infusion, 0.03 $\mu$g/kg per minute i.v. This dose of isoproterenol shortens sinus cycle length by approximately 25%.\textsuperscript{12,14} This same dose of isoproterenol was also used for all antiarrhythmic drug trials.

**Definitions**

The sinus cycle length was averaged over 10 seconds. The ventricular effective and functional refractory periods, QRS duration, and QT interval were determined during pacing at the right ventricular apex at a cycle length of 400 msec and a paper speed of 100 mm/sec. The QT interval was not corrected for rate. The QT interval was measured from the onset of the QRS to the end of the T wave measured in surface lead aVF or II. The ventricular effective refractory period was defined as the longest $S\text{,}S_1$ at which $S_1$ reproducibly did not result in ventricular capture. The interval between the last ventricular depolarization of the drive train and the ventricular depolarization after the extrastimulus ($V_2\text{,}V_2$) was measured from the first rapid deflection in the respective ventricular electrograms, and the ventricular functional refractory period was defined as the shortest obtainable $V_2\text{,}V_3$ interval. The QRS duration was measured in lead aVF or II because the onset and offset are most clearly defined in these leads during right ventricular apical pacing. The pacing spike was used as the onset of the QRS duration to improve the accuracy of measurement.\textsuperscript{15} The QRS duration was measured from the eighth paced complex of the drive train and was averaged from three drive trains (rounded to the closest 5-msec interval) at or near those during which the effective refractory period was determined (i.e., after multiple drive trains introduced). The mode of VT induction was defined according to the number of extrastimuli (in sinus rhythm or after a pacing drive train) required to induce VT. There was no difference in this classification based on pacing cycle length. VT induction with two extrastimuli at pacing cycle lengths of 600 or 400 msec would be classified as a $V_2\text{,}V_2$ induction (Figures 1 and 2). The VT cycle length was averaged from four complexes 15 seconds into the episode of sustained VT. In patients with multiple inducible VT morphologies, one morphology was chosen to compare VT cycle length and the mode of tachycardia induction. Hemodynamic stability was defined as the patient’s ability to tolerate VT without loss of consciousness or other significant symptoms.

**Drug Studies**

The programmed ventricular stimulation protocol was repeated in 22 patients during 31 antiarrhythmic drug trials. Eighteen patients received intravenous procainamide, 13 patients received oral quinidine, and nine patients received both drugs. For intravenous procainamide studies, the antiarrhythmic drug–free isoproterenol infusion was discontinued, and the heart rate was allowed to return to baseline state. Procainamide then was given as a loading infusion of 15–20 mg/kg at a rate not exceeding 50 mg/min. Programmed ventricular stimulation was then begun 10 minutes after the loading dose. After programmed ventricular stimulation was performed during procainamide, isoproterenol was again infused intravenously (0.03 $\mu$g/kg per minute), and after 10 minutes, electrophysiological testing was repeated.

For oral quinidine, testing was performed after at least five doses of the drug. The dose of quinidine was
Results

Patient Characteristics

Twenty-five subjects (22 men and three women) with a mean age of 63 years (range, 33–81 years) were evaluated. The spontaneous arrhythmia in 21 patients was sustained VT, in three patients was syncope, and one patient was a cardiac arrest survivor. Twenty-three patients had coronary artery disease with previous myocardial infarction, and seven of these had a left ventricular aneurysm. One patient (No. 18) had cardiomyopathy, and one patient (No. 25) had segmental wall motion abnormality without coronary artery obstruction. The mean radionuclide left ventricular ejection fraction was 34±12% (range, 14–55%). All patients remained hemodynamically stable and tolerated isoproterenol infusion without adverse affects.

Ventricular Tachycardia Induction

Isoproterenol affected VT induction at control study in 11 of 25 patients (Figure 1). In two patients, the number of ventricular extrastimuli required for VT induction was increased. VT in patient 25 (the patient with segmental wall motion abnormality without coronary obstruction) became noninducible. This patient’s VT had been induced seven times on two separate days before isoproterenol infusion. In nine patients, fewer ventricular extrastimuli were required for VT induction. In patients 10, 19, and 24, VT occurred spontaneously after beginning isoproterenol, and in patient 24, VT could not be terminated until the isoproterenol infusion was discontinued. There was no change in the number of extrastimuli required for VT induction in the remaining 14 patients. Overall, in patients with reproducibly inducible, hemodynamically stable VT, the addition of isoproterenol did not change the number of extrastimuli required to induce VT ($\chi^2$, $p=NS$).

Thirty-one drug trials were performed in 22 patients. Patients 4, 24 (the patient with spontaneous incessant VT during isoproterenol administration), and 25 (the patient whose VT became noninducible) did not undergo further electrophysiological testing with isoproterenol while receiving procainamide or quinidin.

After procainamide infusion, the number of extrastimuli required for VT induction was increased in two patients, decreased in 11 patients, and unchanged in five patients (Figure 2A). Overall, the mode of VT induction after procainamide infusion required fewer ventricular extrastimuli ($n=18$; $\chi^2$; $p=0.018$). During oral quinidine therapy, the number of extrastimuli required for VT induction was increased in three patients, decreased in four patients, and unchanged in six patients (Figure 2B). Overall, the mode of VT induction was unchanged during oral quinidine ($n=13$; $\chi^2$; $p=NS$).

When isoproterenol was administered after intravenous procainamide, the number of extrastimuli required for VT induction was increased in one patient, decreased in 13 patients, and unchanged in four patients (Figure 2A). There was a tendency toward fewer extrastimuli for VT induction during the isoproterenol infusion in the presence of procainamide ($\chi^2$, $p=0.055$). When isoproterenol was administered during oral quinidine therapy, the number of extrastimuli required for VT induction was increased in two patients, decreased in six patients, and unchanged in five patients (Figure 2B).
Overall, isoproterenol did not change the number of extrastimuli required to induce VT during oral quinidine therapy ($\chi^2$, $p=NS$).

**Electrophysiological Parameters**

The sinus cycle length, QT interval and QRS duration during ventricular pacing (cycle length, 400 msec), the ventricular effective and functional refractory periods (cycle length, 400 msec), and VT cycle length were shortened during isoproterenol administration before antiarrhythmic therapy (25 patients; paired $t$ test) (sinus cycle length, 792±37 to 568±18 msec, $p<0.001$; QT, 386±8 to 348±6 msec, $p<0.001$; QRS, 185±4 to 182±4 msec, $p=0.014$; ventricular effective refractory period, 238±5 to 208±4 msec, $p<0.001$; ventricular functional refractory period, 261±6 to 227±5 msec, $p<0.001$; VT cycle length, 311±9 to 291±9 msec, $p<0.001$).

The sinus cycle length and QT interval during ventricular pacing were also shortened by isoproterenol during antiarrhythmic therapy. The sinus cycle length and the QT interval were shortened by an equal degree during isoproterenol before and during procainamide and quinidine (ANOVA interaction, $p=NS$) (Table 1).

**Refractory Periods**

The right ventricular effective refractory period was significantly decreased by isoproterenol (ANOVA, isoproterenol effect) both before (procainamide group, $n=17$, 231±5 to 199±4 msec; quinidine group, $n=13$, 242±8 to 215±5 msec) and during antiarrhythmic drug therapy (procainamide group, $n=17$, 254±6 to 214±5 msec, $p=0.0001$; quinidine group, $n=13$, 278±7 to 243±8 msec, $p=0.0001$) (Figure 3). The least mean squares were determined to assess the significance of individual comparisons. The ventricular effective refractory period was decreased by isoproterenol before (procainamide group, $p=0.0001$; quinidine group, $p=0.0003$) and during antiarrhythmic drug therapy (procainamide group, $p=0.0001$; quinidine group, $p=0.0001$). The decrease during isoproterenol was similar before and after antiarrhythmic drugs (ANOVA interaction, $p=NS$ for both groups); that is, the slopes of the lines in Figure 3 are similar. Examined differently, the decrease in effective refractory period during isoproterenol was not different between the drug-free state and the states of the procainamide-treated ($n=17$, 32±5 versus 39±6 msec, $p=NS$) or quinidine-treated groups ($n=13$, 27±6 versus 35±5 msec, $p=NS$) (paired $t$ test) (Figure 4) as an absolute change or when normalized for preisoproterenol effective refractory period (procainamide group, 13±2.1% versus 15±2.1%, $p=NS$; quinidine group, 11±2.2% versus 12.5±1.8%, $p=NS$). Similar observations were made for ventricular functional refractory period (Table 1).

The ventricular effective refractory period was significantly increased by antiarrhythmic therapy both before
and during isoproterenol infusion (ANOVA antiarhythmic drug effect: procainamide, \(p=0.0002\); quinidine, \(p=0.0001\)) (Figure 3). When individual comparisons were performed (least mean squares), the ventricular effective refractory period was increased by antiarrhythmic drugs both before (procainamide group,
group, \( p=0.07 \) and during antiarrhythmic drug therapy (procainamide group, \( p=0.0001 \); quinidine group, \( p=0.0001 \)). The decrease in QRS duration was greater during both procainamide (ANOVA interaction, \( p=0.0001 \)) and quinidine (ANOVA interaction, \( p=0.02 \)) than in the drug-free state; that is, the slopes of the lines representing antiarrhythmic drug therapy in Figure 5 are steeper than in the drug-free state. Examined differently, the decrease in QRS duration during isoproterenol infusion was greater during both procainamide (\( n=17, 21±2 \) versus \( 5±2 \) msec, \( p<0.001 \)) and quinidine (\( 15±3 \) versus \( 5±2 \) msec, \( p=0.02 \) (\( t \) test) (Figure 4) than in the drug-free state. When this difference is normalized for preisoproterenol QRS duration, the results remain significant (procainamide group, 9.5±1.0% versus 2.6±1.0%, \( p<0.001 \); quinidine group, 6.5±1.5% versus 2.5±0.8%, \( p=0.03 \)).

The QRS duration was increased by antiarrhythmic therapy both before and during isoproterenol infusion (ANOVA antiarrhythmic drug effect: procainamide, \( p=0.0001 \); quinidine, \( p=0.0003 \)) (Figure 5). When individual comparisons were performed (least mean squares), the QRS duration was increased by antiarrhythmic drugs both before (procainamide group, \( p=0.0001 \); quinidine group, \( p=0.0001 \)) and during isoproterenol infusion (procainamide group, \( p=0.0001 \); quinidine group, \( p=0.0001 \)). In the nine patients who received both procainamide and quinidine, the increase in QRS duration was the same with these two antiarrhythmic drugs both before (procainamide, 34±7 msec; quinidine, 36±7 msec) and during isoproterenol infusion (procainamide, 22±6 msec; quinidine, 26±8 msec; ANOVA antiarrhythmic drug effect, \( p=NS \)). The increase in QRS duration with antiarrhythmic drug therapy was less during isoproterenol infusion (ANOVA isoproterenol effect, \( p=0.007 \)).

**Ventricular Tachycardia Cycle Length**

The VT cycle length was decreased by isoproterenol (ANOVA isoproterenol effect) both before (procainamide group, \( n=18, 314±11 \) to \( 291±11 \) msec; quinidine group, \( n=12, 298±10 \) to \( 280±9 \) msec) and during antiarrhythmic drug therapy (procainamide group, 422±15 to 359±11 msec, \( p=0.0001 \); quinidine group, 415±14 to 355±10 msec, \( p=0.0001 \)) (Figure 6). The least mean squares were determined to assess the significance of individual comparisons. The VT cycle length was decreased by isoproterenol before (procainamide group, \( p=0.001 \); quinidine group, \( p=0.018 \)) and during antiarrhythmic drug therapy (procainamide group, \( p=0.0001 \); quinidine group, \( p=0.0001 \)). The decrease in VT cycle length was greater during both procainamide (ANOVA interaction, \( p=0.0001 \)) and quinidine (ANOVA interaction, \( p=0.001 \)) than in the drug-free state; that is, the slopes of the lines representing antiarrhythmic drug therapy in Figure 6 are steeper than in the drug-free state. Examined differently, the decrease in VT cycle length during isoproterenol infusion was greater during both procainamide (\( n=18, 63±7 \) versus 23±6 msec, \( p<0.001 \)) and quinidine (\( n=12, 59±8 \) versus 18±5 msec, \( p=0.001 \) (\( t \) test) than in the drug-free state (Figure 4). When this difference is normalized for preisoproterenol VT cycle length, the results remain significant (procainamide, 14.5±1.2% versus 7.2±1.9%, \( p=0.002 \); quinidine, 13.9±1.7% versus 2.5±0.8%, \( p=0.03 \)).
6.7±1.8%, p=0.01). These normalized results indicate that the longer VT cycle length during antiarrhythmic drug therapy was not responsible for the larger absolute changes in cycle length seen during isoproterenol administration.

The VT cycle length was increased by antiarrhythmic therapy both before and during isoproterenol infusion (ANOVA antiarrhythmic drug effect: procainamide, p=0.0001; quinidine, p=0.0001) (Figure 6). When individual comparisons were performed (least mean squares), the VT cycle length was increased by antiarrhythmic drugs both before (procainamide group, p=0.0001; quinidine group, p=0.0001) and during isoproterenol infusion (procainamide group, p=0.0001; quinidine group, p=0.0001). In the nine patients who received both procainamide and quinidine, the increase in VT cycle length was the same with these two antiarrhythmic drugs both before (procainamide, 102±12 msec; quinidine, 122±15 msec) and during isoproterenol infusion (procainamide, 68±9 msec; quinidine, 84±12 msec; ANOVA antiarrhythmic drug effect, p=NS). The increase in VT cycle length with antiarrhythmic drugs was less during isoproterenol administration (ANOVA isoproterenol effect, p=0.0014).

There was no correlation between the decrease (absolute or percentage) in ventricular effective refractory period and the decrease in VT cycle length with isoproterenol, nor was there a correlation between the increase (absolute or percentage) in ventricular effective refractory period and the increase in VT cycle length during procainamide or quinidine therapy. A statistically significant correlation was also not present between changes in QRS duration and VT cycle length (absolute or percentage), although the changes in mean QRS duration and VT cycle length were nearly parallel. Importantly, isoproterenol caused a greater decrease in QRS duration and VT cycle length in the presence of procainamide and quinidine versus the control state, a finding not observed with refractoriness.

**Discussion**

**Major Findings**

The major findings in this study of patients with reproducibly inducible, hemodynamically stable monomorphic VT were that isoproterenol (at a dose that decreased sinus cycle length by a mean of 28%) 1) decreased VT cycle length to a greater degree in the presence of procainamide and quinidine than in the baseline state. Isoproterenol did not completely reverse the antiarrhythmic drug–induced slowing of VT; 2) decreased QRS duration to a greater degree in the presence of procainamide and quinidine than in the baseline state. Isoproterenol did not completely reverse the antiarrhythmic drug–induced increase in QRS duration; 3) decreased right ventricular refractoriness to the same degree in the baseline state and during procainamide and quinidine therapy. Isoproterenol did not completely reverse the antiarrhythmic drug–induced increase in ventricular refractoriness; and 4) had no significant effect on the mode of VT induction in the drug-free state and minimal effect in the presence of procainamide and quinidine.
Ventricular Tachycardia Cycle Length

Few data are available that assess the effects of isoproterenol on inducible sustained VT cycle length. Previous studies in a canine myocardial infarction model demonstrated that isoproterenol decreased VT cycle length in both the acute (within 24 hours) and chronic (after 3–5 days) infarction periods. One study showed in a subgroup of six patients that VT cycle length determined before and during epinephrine infusion in the absence of antiarrhythmic drugs shortened from 324 to 287 msec. In our patients, the tissues in the presumed reentrant circuit were sensitive to the effects of β-adrenergic stimulation. The VT cycle length was decreased by isoproterenol to a greater extent both absolutely and on a percentage basis during drug therapy, but the drug-induced slowing of VT was not completely reversed.

Similar interactions between isoproterenol and antiarrhythmic agents have been noted in patients with atrioventricular reentry in which the tachycardia circuit is clearly defined. In this circumstance, isoproterenol minimally alters conduction over the accessory pathway in the absence of drug therapy but can substantially inhibit antiarrhythmic drug–induced depression of conduction and prolongation of refractoriness of the accessory pathway.

Ventricular Tachycardia cycle length and refractoriness.

In the present study, the ventricular refractory periods were decreased by isoproterenol but in contrast to VT cycle length, the decrease was the same before and during antiarrhythmic drug therapy (Figures 3, 4, and 6). Furthermore, the increase in QRS duration and VT cycle length was the same during intravenous procainamide and oral quinidine therapy (Figures 5 and 6), but the increase in ventricular effective refractory period was greater during quinidine than procainamide therapy (Figure 3). These observations suggest that the isoproterenol-induced decrease in refractoriness was not the mechanism for the observed changes in VT cycle length and indirectly argue against an increase in refractoriness as the primary cause of the slower VT rate during drug therapy.

Ventricular tachycardia cycle length and conduction.

Reentry was the likely mechanism for VT in our patients. An excitable gap was demonstrated in 20 of 25 patients with one or two ventricular extrastimuli, although complete reset curves were not performed. However, the patients were similar to those in other studies of VT (previous infarction, monomorphic VT) in which a fully excitable gap has been demonstrated, implying reentry around a fixed anatomic defect. In this model of reentry, changes in cycle length are primarily due to changes in conduction velocity. However, it is also possible that all or part of the reentrant circuit is made up of a line of functional block that is present during the tachycardia but not during sinus...
rhythm.³¹ In this instance, isoproterenol may decrease the area of functional block or alter the return pathway (without affecting the exit site) and thus decrease the length of the reentrant circuit, causing a decrease in VT cycle length. We used QRS duration during ventricular pacing as a global index of conduction velocity. Similar to the VT cycle length, the QRS duration decreased with isoproterenol to a greater degree in the presence of procainamide and quinidine than in the drug-free state. This suggests but does not show conclusively that the observed changes were due to effects on conduction within the VT circuit.

Previous data are consistent with this hypothesis. Marchlinski et al."¹⁵ demonstrated a linear correlation between the change from control in QRS duration noted during right ventricular pacing (using a cycle length similar to baseline VT cycle length) and VT cycle length in the presence of procainamide. Although we were unable to confirm this correlation, the changes we observed were similar in direction if not magnitude. Because QRS duration is a measure of global ventricular conduction and not necessarily of conduction within the tachycardia circuit, it may not be surprising that a linear correlation between the change in QRS duration and VT cycle length was not present. We assessed QRS duration at a pacing cycle length of 400 msec, and it is possible that we would have demonstrated a better correlation if faster pacing cycle lengths had been used."¹⁵ In another study, Kay et al."²⁹ showed in humans that the increase in VT cycle length with intravenous procainamide was due to slowing of conduction within the VT circuit and that slowing of conduction in the circuit was greater than in normal myocardium. Thus, our data support the hypothesis that the changes in VT cycle length with procainamide and quinidine as well as with isoproterenol are due primarily to changes in conduction and not refractoriness.

Potential Mechanism

Previous data indicate that cells with normal and abnormal action potentials, both depressed fast and slow responses, exist in resected human ventricular myocardium that appeared to participate in VT."³² In normal ventricular tissue, isoproterenol has little effect on conduction velocity. However, in abnormal ventricular tissue with decreased dV/dt and action potential amplitude, isoproterenol can restore these toward normal, resulting in more rapid conduction velocity."³³,³⁴ It is possible that the observed decrease in VT cycle length demonstrated in the drug-free state may have occurred through this effect of isoproterenol on the areas of slow conduction within the VT circuit. Procainamide and quinidine block cardiac potassium and sodium channels, resulting in a prolongation of refractoriness and a slowing of conduction."³⁴ Both agents prolonged refractoriness and slowed conduction in the ventricles of our patients. In cellular preparations, isoproterenol enhances the outward potassium currents, resulting in a decrease in action potential duration and a decrease in refractoriness"³⁵ and thus may partially reverse the antiarrhythmic drug–induced potassium channel blockade. In contrast to the control state, isoproterenol substantially reversed the increase in QRS duration and the slowing of VT caused by procainamide and quinidine in our patients. Since the drug-induced slowing of conduction is greatest in abnormal tissue,"²⁹,³⁶ and isoproterenol speeds conduction in abnormal tissue,"³³,³⁴ it is possible that the isoproterenol-induced enhancement of conduction during procainamide and quinidine therapy occurs by partial reversal of sodium channel blockade of the abnormal tissues of the VT circuit.

It should be pointed out that the effects of isoproterenol may be the result of changes in cell-to-cell coupling. Although we do not know if conduction in the VT circuits of our patients was anisotropic, it has been demonstrated that procainamide decreases conduction velocity to a greater degree during propagation of impulses longitudinal to fiber orientation rather than in a transverse direction."³⁷ The observed effects of isoproterenol may be due to a reversal of antiarrhythmic drug effect on cell coupling. This may be modulated by changes of intracellular cAMP or calcium."³⁸

Ventricular Tachycardia Induction

Isoproterenol may be necessary to initiate VT in patients with exercise-induced VT"¹⁻⁴ or non–exercise-related VT with or without programmed ventricular stimulation."⁵⁻⁷ Two studies have evaluated the use of catecholamine infusion as a method of improving the predictive value of programmed ventricular stimulation during the assessment of antiarrhythmic drug efficacy."¹⁰,³⁹ The effects of isoproterenol in humans on the induction of sustained VT not requiring isoproterenol for initiation have not been previously evaluated. In our patients who did not require isoproterenol for initiation of VT, it is interesting that the mode of VT induction was minimally changed in the presence of isoproterenol. Of particular importance was the observation that VT could no longer be induced during isoproterenol infusion in one patient, whereas it had been reproducibly initiated on many occasions in the drug-free control state. This most likely is due to decreased refractoriness, decreased dispersion of refractoriness, or accelerated conduction in the tissues of the reentrant circuit that precluded induction of tachycardia.

Limitations

The results of this study imply that changes in conduction velocity are responsible for the change in VT cycle length with isoproterenol and the antiarrhythmic drugs procainamide and quinidine. However, conduction and refractoriness could not be measured directly in the tachycardia circuit. The measurement of conduction (QRS duration) and right ventricular refractoriness are primarily from normal tissue; the effects in the presumably abnormal tissue that makes up the VT circuit may be different.

This study was performed in a group of patients selected for hemodynamically stable, sustained VT that was reproducibly inducible in the absence of isoproterenol. It is possible that patients with hemodynamically unstable VT or those patients who require isoproterenol to induce VT may respond differently. VT remained inducible in all patients except one receiving quinidine. Therefore, the effects of isoproterenol were determined in a drug-resistant population that may not be indicative of the effects of isoproterenol in a more general group of patients with ventricular arrhythmias.
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