Cisapride-Induced Transmural Dispersion of Repolarization and Torsade de Pointes in the Canine Left Ventricular Wedge Preparation During Epicardial Stimulation

José M. Di Diego, MD; Luiz Belardinelli, MD; Charles Antzelevitch, PhD

Background—Cisapride, a gastrointestinal prokinetic agent, was recently withdrawn from the market because of its propensity to induce torsade de pointes (TdP) arrhythmias. The present study examines the electrophysiological actions of cisapride in the isolated arterially perfused canine left ventricular wedge preparation.

Methods and Results—Transmembrane action potentials from epicardial and M regions and a pseudo-ECG were simultaneously recorded. Cisapride (0.1 to 5 μmol/L) was added to the coronary perfusate. Cisapride prolonged the QT interval and increased transmural dispersion of repolarization (TDR) at relatively low but not at high concentrations. TdP could be induced with programmed electrical stimulation only at a low concentration of drug (0.2 μmol/L), when TDR was maximally prolonged. Moreover, TdP could only be induced during epicardial (but not endocardial) activation of the wedge, which was found to augment TDR. At higher concentrations of cisapride, QT was further prolonged, TDR was diminished, and TdP could no longer be induced. T_peak–T_end interval and T_peak–T_end area provided reasonable electrocardiographic indices of TDR.

Conclusion—Our data (1) demonstrate a biphasic concentration/response relationship for the effect of cisapride to induce long-QT syndrome and TdP, (2) show the value of the left ventricular wedge preparation in identifying drugs that pose an arrhythmic risk, (3) support the hypothesis that risk for development of TdP is related to the increase in TDR rather than to prolongation of the QT interval, and (4) indicate that epicardial activation of the left ventricle, as occurs during biventricular pacing, can facilitate the development of TdP under long-QT conditions. (Circulation. 2003;108:1027-1033.)

Key Words: long-QT syndrome ▪ arrhythmias ▪ drugs ▪ ventricles ▪ pacing

Cisapride, a piperidinyl benzamide gastrointestinal prokinetic agent, was withdrawn from the market in the United States in July 2000 because of its propensity to prolong the QT interval and lead to life-threatening torsade de pointes (TdP) arrhythmias. Cisapride was the fifth drug to be withdrawn from the market in the span of 3 years, highlighting a growing problem and the need to better identify drugs with a proclivity to induce TdP during preclinical and clinical stages of development. The present study was designed to determine the electrophysiological actions of cisapride in the canine isolated arterially perfused left ventricular wedge preparation, an experimental model previously shown to develop TdP arrhythmias in response to QT-prolonging agents capable of augmenting transmural dispersion of repolarization (TDR).

Recent studies have demonstrated that biventricular pacing, a technique that has gained popularity for the treatment of heart failure, may place individuals predisposed to long-QT syndrome (LQTS) at risk for the development of TdP. The mechanism proposed involves the exaggeration of TDR as a consequence of epicardial (EPI) activation of the left ventricle (coronary sinus lead). We provide a test of this hypothesis by assessing the effect of cisapride on QT, TDR, and ability to induce TdP with either endocardial or EPI stimulation.

Methods

Dogs weighing 20 to 25 kg were anticoagulated with heparin and anesthetized with sodium pentobarbital (30 to 35 mg/kg IV). The chest was opened via a left thoracotomy, and the heart was excised, placed in Tyrode's solution, and transferred to a dissection tray. Transmural left ventricular wedges with dimensions of ~12×30×12 mm were dissected from the mid-to-apical anterior region of the left ventricular wall, and a diagonal branch of the left anterior descending coronary artery was cannulated and perfused by using Tyrode's solution. The composition of the Tyrode's solution was (in mmol/L) as follows: NaCl 129, KCl 4, NaH₂PO₄ 0.9, NaHCO₃ 20, CaCl₂ 1.8, MgSO₄ 0.5, and D-glucose 5.5 (pH 7.4).
Transmembrane action potentials were recorded from EPI and subendocardial (M) regions by using floating microelectrodes. A transmural pseudo-ECG was recorded by using 2 AgCl half-cells placed ~1 cm from the EPI(+) and endocardial (−) surfaces of the preparation and along the same axis as the transmembrane recordings.

Ventricular wedges were allowed to equilibrate in the chamber for 2 to 3 hours while paced at basic cycle lengths (BCLs) of 2000 ms by using silver bipolar electrodes placed in contact with the endocardial surface. The temperature of the perfusate was maintained at 35°C to 35.5°C. Cisapride was dissolved in 100% dimethyl sulfoxide (stock solution, 5 mmol/L) and added to the perfusate in increasing concentrations (0.1 to 5.0 μmol/L) at 30- to 40-minute intervals. Dimethyl sulfoxide (0.1%; concentration of DMSO at highest concentration of cisapride [5 μmol/L] used in the study) was previously shown to have no effect on the electrophysiology of the wedge preparation.

**Statistics**

Summary data are reported as mean±SEM. Statistical analysis was performed by using either unpaired \( t \) test or ANOVA coupled with Dunnett’s test, as appropriate.

**Results**

Figure 1 shows the effect of 1 μmol/L cisapride on the ECG and action potential morphology of M and EPI cells recorded from a left ventricular wedge preparation stimulated from either endocardial or EPI sites at a BCL of 2000 ms. Cisapride prolonged QT interval from 309 to 332 ms and produced a greater prolongation of action potential duration (APD) in M versus EPI cells, resulting in an increase in TDR (Figure 1A). When basic stimulation was applied to epicardium (Figure 1B), QT and TDR were longer under control conditions and were further increased after the addition of cisapride. The interval between the peak and end of the T wave of the ECG (\( T_{\text{peak}}-T_{\text{end}} \)) and the area under this segment of the T wave (area), parameters previously shown to provide an ECG index of TDR, increased in parallel with the change in TDR. In the case of EPI stimulation, QT and \( T_{\text{peak}}-T_{\text{end}} \) increased from 66 and 59 ms to 83 and 77 ms, respectively, in response to 1 μmol/L cisapride. Composite data for the concentration-dependent effects of cisapride on these parameters are presented in Figure 2 and the Table. Cisapride produced a biphasic effect, progressively increasing QT, TDR, \( T_{\text{peak}}-T_{\text{end}} \), and area at relatively low concentrations. Higher concentrations of the drug produced a progressively smaller effect on these parameters. All repolarization parameters were larger, and the concentration-dependent effects of the drug were considerably more prominent during EPI versus endocardial stimulation.

Figure 1. Electrophysiological effects of cisapride. From top to bottom, Action potentials recorded from the M region and EPI, and the ECG recorded from a left ventricular wedge preparation. BCL=2000 ms. Each panel depicts superimposed traces recorded at baseline conditions (control) and at 30 minutes after addition of 1 μmol/L cisapride. A, Endocardial stimulation. B, Epicardial stimulation.
increase in TDR. Cisapride also produced a concentration-dependent prolongation of transmural conduction time, consistent with an effect of the drug to block inward currents at the higher concentrations. The inhibition of inward currents is also likely responsible for the reversal of the effects of cisapride on repolarization parameters at higher concentrations (Figure 3C).

TdP did not develop spontaneously under any condition, nor could it be induced under control conditions or at any concentration of cisapride during endocardial stimulation. The arrhythmia was observed in 2 of 6 wedge preparations at cisapride concentrations of 0.2 \mu M/L. TdP could be elicited with single extrastimuli (S2) applied to epicardium when basic stimulation (S1) was also applied to epicardium but not when basic stimulation was applied to endocardium (Figure 4). Figure 4A shows the effect of programmed electrical stimulation (PES) to induce a single reentrant beat at cisapride concentration of 0.1 \mu M/L (S1–S2 = 194 ms). In the same preparation, PES (S1–S2 = 204 ms) induced polymorphic ventricular tachycardias of varying durations when the concentration of the drug was increased to 0.2 \mu M/L (Figure 4B and 4C). TDR was 90 and 87 ms in the 2 preparations in which TdP could be induced. The arrhythmia could not be induced at higher concentrations of cisapride, despite the effect of the higher doses to further prolong QT.

Figure 5 compares the effect of 0.2 and 1 \mu M/L cisapride on the ECG and action potential morphology of M and EPI cells recorded from the left ventricular wedge preparation illustrated in Figure 4. The wedge was stimulated from an EPI site at a BCL of 2000 ms. Increasing the concentration of cisapride from 0.2 to 1 \mu M/L prolonged the QT interval from 332 to 345 ms but reduced the TDR from 90 to 83 ms. The figure suggests that the failure of cisapride to induce TdP at the higher concentrations is related to its actions to reduce TDR at the higher concentration, supporting the hypothesis that risk for development of TdP is related to the increase in TDR rather than in QT.

**Discussion**

The present study demonstrates, for the first time, the effect of cisapride to prolong the QT interval and increase TDR at relatively low but not high concentrations. TdP could be induced only at a low concentration of the drug (0.2 \mu M/L), at which TDR was maximally prolonged, and only during EPI activation of the wedge, which facilitates the development of a marked increase in TDR.

The electrophysiological effects observed at relatively low concentrations of cisapride are consistent with a selective rapidly activating delayed rectifier (I_{Kr}) blocker. Cisapride, a potent I_{Kr} blocker, produces a preferential prolongation of the APD of the M cell, leading to the development of a large dispersion of action potential duration between the 2 cell types. Recent work from our laboratory has suggested that T_{peak}–T_{end} interval and area underlying this segment of the T wave can provide ECG indices of TDR.\(^3\)\(^4\) The present study provides further support for this hypothesis by showing that these 3 parameters change in parallel. Although we did not observe early afterdepolarizations (EADs) in the wedge preparation, in a parallel study involving tissues isolated from the canine left ventricle, cisapride was observed to induce EADs in tissues isolated from the M region but not epicardium (data not shown). EADs may provide the extrasystole that triggers spontaneous TdP. Thus, cisapride induces electrophysiological changes that provide both the substrate (increase in TDR) and trigger (EAD) for the generation of TdP arrhythmias.

When transmural activation was reversed (EPI stimulation) TDR was further increased. The increase in TDR is due to
Effect of Cisapride in the Canine LV Wedge: \( \text{APD}_{90} \) of M and EPI, QT Interval, \( T_{\text{peak}}-T_{\text{end}} \), TDR, and Area

<table>
<thead>
<tr>
<th>BCL = 2000 ms</th>
<th>EPI</th>
<th>M</th>
<th>QT Interval, ms</th>
<th>( T_{\text{peak}}-T_{\text{end}} ), ms</th>
<th>TDR, ms</th>
<th>Area, mV \cdot ms</th>
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<tbody>
<tr>
<td>Endo stimulation (n=6 wedges, LV)</td>
<td>233.8±10.6</td>
<td>279.0±5.0</td>
<td>306.3±5.7</td>
<td>40.66±2.8</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
<td></td>
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<tr>
<td>Control</td>
<td>233.8±10.6</td>
<td>279.0±5.0</td>
<td>306.3±5.7</td>
<td>40.66±2.8</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>0.1 ( \mu )mol/L</td>
<td>253.7±10.4</td>
<td>307.0±8.5</td>
<td>331.1±8.4</td>
<td>48.8±4.1</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>0.2 ( \mu )mol/L</td>
<td>266.8±7.3</td>
<td>325.3±6.0</td>
<td>347.6±6.1</td>
<td>52.6±5.0</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>0.5 ( \mu )mol/L</td>
<td>277.8±5.4</td>
<td>333.3±7.0</td>
<td>352.8±7.8</td>
<td>48.9±5.4</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<td>1 ( \mu )mol/L</td>
<td>275.5±8.7</td>
<td>329.0±7.4</td>
<td>349.6±8.4</td>
<td>46.8±3.6</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>5 ( \mu )mol/L</td>
<td>263.8±4.5</td>
<td>313.3±6.8</td>
<td>327.8±5.2</td>
<td>40.6±2.5</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<th>BCL = 500 ms</th>
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<th>M</th>
<th>QT Interval, ms</th>
<th>( T_{\text{peak}}-T_{\text{end}} ), ms</th>
<th>TDR, ms</th>
<th>Area, mV \cdot ms</th>
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<tbody>
<tr>
<td>Endo stimulation (n=6 wedges, LV)</td>
<td>234.3±9.8</td>
<td>278.1±5.6</td>
<td>322.6±11.5</td>
<td>64.8±5.7</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>Control</td>
<td>234.3±9.8</td>
<td>278.1±5.6</td>
<td>322.6±11.5</td>
<td>64.8±5.7</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>0.1 ( \mu )mol/L</td>
<td>246.0±6.4</td>
<td>299.0±9.5</td>
<td>346.2±11.1</td>
<td>71.6±4.4</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>0.2 ( \mu )mol/L</td>
<td>259.5±12.6</td>
<td>315.5±8.9</td>
<td>361.7±10.7</td>
<td>81.2±5.7</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>0.5 ( \mu )mol/L</td>
<td>279.8±5.5</td>
<td>336.0±5.0</td>
<td>365.0±9.2</td>
<td>71.0±3.0</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>1 ( \mu )mol/L</td>
<td>277.4±8.0</td>
<td>331.2±7.7</td>
<td>360.0±5.3</td>
<td>73.2±3.9</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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<tr>
<td>5 ( \mu )mol/L</td>
<td>257.0±5.2</td>
<td>296.3±6.3</td>
<td>343.7±3.6</td>
<td>63.6±4.6</td>
<td>( *P&lt;0.01 ) vs EPI stimulation; ( †P&lt;0.05 ) vs EPI stimulation; ( ‡P&lt;0.05 ) vs control; and ( §P&lt;0.001 ) vs EPI stimulation.</td>
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At higher concentrations, the effects of cisapride on QT, APD, and TDR decreased, and TdP could no longer be induced by PES. This is most likely because of the effect of cisapride to additionally block inward currents at these higher concentrations. This observation is consistent with the effect of the drug to slow conduction at these concentrations. Antiarrhythmic drugs that block \( \text{I}_{\text{Ks}} \), but fail to prolong QT and/or induce TdP have in common the ability to inhibit a combination of inward and outward currents \( (\text{I}_{\text{Na}}, \text{I}_{\text{Ca}}, \text{I}_{\text{Ks}}, \text{I}_{\text{C}}, \text{I}_{\text{Cl}}) \). The lack of QT prolongation is the result of a reduction in outward current that is countered by a reduction in inward current, thereby causing little or no change in net repolarizing current.5

Figure 3. Concentration-dependent effects of cisapride on repolarization and conduction parameters during EPI versus endocardial (Endo) stimulation.
Our results also demonstrate the value of the left ventricular wedge preparation in identifying drugs that may pose an arrhythmic risk during preclinical studies, even when that risk is relatively small, as in the case of cisapride. Drug-induced \( I_{Kr} \) block and QT prolongation have attracted considerable attention in recent years because of the association of \( I_{Kr} \) and QT interval prolongation in the ECG with life-threatening cardiac arrhythmias, such as TdP.6 An ever-increasing number of noncardiovascular agents have also been shown to aggravate and/or precipitate TdP.6 More than 50 commercially available or investigational noncardiovascular and 20 cardiovascular nonantiarrhythmic drugs have been implicated. This problem appears to arise more frequently with newer drugs, and a number of agents have been withdrawn from the market in recent years (eg, prenylamine, terodiline, and, in some countries, terfenadine, astemizole, and cisapride).

Drug-induced TdP has been shown to develop largely as a consequence of an increase in dispersion of ventricular repolarization secondary to amplification of electrical heterogeneities intrinsic to ventricular myocardium.5,7–10 Studies published over the past dozen years have demonstrated that ventricular myocardium is comprised of at least 3 electrophysiologically distinct cell types: EPI, M, and endocardial.5,11 The 3 ventricular myocardial cell types differ principally with regard to phase 1 and phase 3 repolarization characteristics. M cells are distinguished by the ability of their action potential to prolong disproportionately relative to the action potential of other ventricular myocardial cell types in response to a slowing of rate and/or in response to drugs with QT-prolonging actions.5,12 The ionic basis for these features include the presence of a smaller slowly activating delayed rectifier current (\( I_{Ks} \)),13 a larger late sodium current (late \( I_{Na} \)),14 and a larger electrogenic sodium–calcium exchange current (\( I_{Na-Ca} \)).15 The densities of the rapidly activating delayed rectifier (\( I_{Kr} \)) and inward rectifier (\( I_{K1} \)) currents are similar in the 3 transmural cell types.
M cells are similar to EPI and endocardial cells histologically, but electrophysiologically and pharmacologically, they appear to be a hybrid between Purkinje and ventricular cells. Similar to Purkinje fibers, they develop EADs in response to agents and pathophysiological conditions that reduce the repolarization reserve of the ventricular myocardium. Epicardium and endocardium do not. EADs are thought to give rise to the extrastyles that trigger TdP.

Most drugs that prolong the QT interval also increase transmural heterogeneity of final repolarization by causing a preferential prolongation of the action potential of M cells.\textsuperscript{5,7–10} \(I_K\) blockers, including d-sotalol, almokalant, E-4031, and erythromycin, augment TDR in this way. A similar preferential prolongation of the M-cell APD is seen with agents that increase calcium current (\(I_{Ca}\)) such as Bay K 8644, as well as with agents that increase late \(I_{Ks}\) such as ATX-II and anthopleurin-A. A more complex situation exists with drugs affecting \(\pm 2\) ion channels, such as quinidine, pentobarbital, amiodarone, and azimilide. In the case of quinidine, relatively low therapeutic levels of the drug (3 to 5 \(\mu\)mol/L; 1.14 to 1.89 \(\mu\)g/mL), produce a marked prolongation of the M-cell APD but not of epicardium and endocardium, consistent with a predominant effect of the drug to block \(I_{Ks}\) at this concentration.\textsuperscript{16} At higher concentrations (10 to 30 \(\mu\)mol/L; 3.78 to 11.37 \(\mu\)g/mL), quinidine produces a further prolongation of the EPI and endocardial action potential, consistent with an effect of the drug to block \(I_{Ks}\), and abbreviation of the APD of the M cell, because of its action to suppress late \(I_{Ks}\).\textsuperscript{17} Voltage clamp studies have shown that low concentrations of quinidine potently block \(I_{Ks}\) but not \(I_{Kt}\), whereas higher concentrations potently block both \(I_{Ks}\) and \(I_{Kt}\).\textsuperscript{7} Indeed, in experimental models, high concentrations of quinidine have little to no effect to prolong QT because of the potent effect of the drug to block late \(I_{Ks}\). The antiischemic agent ranolazine is another agent recently shown to block \(I_{Ks}\) and \(I_{Kt}\), but it fails to produce substantial QT prolongation because of the concomitant actions of the drug to block late \(I_{Ks}\).\textsuperscript{18}

Sodium pentobarbital prolongs the QT interval but reduces TDR\textsuperscript{19} by inhibiting \(I_{Ks}\), \(I_{Kt}\), and \(I_{Ko}\), thus leading to a greater prolongation of APD in EPI and endocardial cells than in M cells and a reduction in the TDR. The drug also suppresses d-sotalol–induced EAD activity in M cells. Thus, despite its actions to prolong QT, pentobarbital does not induce TdP. By virtue of its actions to reduce transmural dispersion and inhibit EAD-induced triggered activity, the anesthetic is effective in suppressing d-sotalol–induced TdP.\textsuperscript{20}

Amiodarone is another agent that prolongs QT but does not typically induce TdP. In addition to its \(\beta\)-blocking properties, amiodarone is known to block the sodium, potassium, and calcium channels in the heart. When administered chronically, amiodarone produces a greater prolongation of action potential duration in epicardium and endocardium of the dog heart, but less of an increase, or even a decrease at slow rates, in the M region, thereby reducing TDR.\textsuperscript{16} Chronic amiodarone therapy also suppresses the ability of the \(I_{Ks}\) blocker d-sotalol to increase TDR or induce EADs. Similar results have recently been reported with chronic amiodarone in the chronic AV block dog model.\textsuperscript{21} TdP did not develop, nor could it be induced, even though QT prolonged significantly in response to chronic amiodarone. The absence of arrhythmias was explained on the basis of the failure of amiodarone to create the substrate for reentry in the form of a dispersion of repolarization across the ventricular wall or septum as well as the absence of the trigger in the form of EADs.

Taken together, these observations indicate that QT prolongation is not the cause of TdP, but rather that it is the increase in dispersion of repolarization, which usually accompanies QT prolongation, that provides the arrhythmogenic substrate.\textsuperscript{5,11} The present study provides additional compelling evidence in support of this hypothesis by demonstrating, in the same preparation, the development of TdP by cisapride at a concentration that maximally increases TDR (0.2 \(\mu\)mol/L), and the failure of TdP to develop after an increase in the concentration of cisapride (0.2 to 1 \(\mu\)mol/L), which reduces TDR despite increasing QT.

Acknowledgments

The present study was supported by grants from the National Institutes of Health (HL47678 to Dr Antzelevitch); American Heart Association, New York State Affiliate (Drs Antzelevitch and Di Diego); and the Masons of New York and Florida.

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Circulation. 2003;108:1027-1033; originally published online August 11, 2003;
doi: 10.1161/01.CIR.0000085066.05180.40
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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