Cellular Basis for the ECG Features of the LQT1 Form of the Long-QT Syndrome

Effects of β-Adrenergic Agonists and Antagonists and Sodium Channel Blockers on Transmural Dispersion of Repolarization and Torsade de Pointes

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Background—This study examines the cellular basis for the phenotypic appearance of broad-based T waves, increased transmural dispersion of repolarization (TDR), and torsade de pointes (TdP) induced by β-adrenergic agonists under conditions mimicking the LQT1 form of the congenital long-QT syndrome.

Methods and Results—A transmural ECG and transmembrane action potentials from epicardial, M, and endocardial cells were recorded simultaneously from an arterially perfused wedge of canine left ventricle. Chromanol 293B, a specific I\textsubscript{Ks} blocker, dose-dependently (1 to 100 \(\mu\text{mol/L}\)) prolonged the QT interval and action potential duration (APD\(_{90}\)) of the 3 cell types but did not widen the T wave, increase TDR, or induce TdP. Isoproterenol 10 to 100 nmol/L in the continued presence of chromanol 293B 30 \(\mu\text{mol/L}\) abbreviated the APD\(_{90}\) of epicardial and endocardial cells but not that of the M cell, resulting in widening of the T wave and a dramatic accentuation of TDR. Spontaneous as well as programmed electrical stimulation (PES)-induced TdP was observed only after exposure to the I\textsubscript{Ks} blocker and isoproterenol. Therapeutic concentrations of propranolol (0.5 to 1 \(\mu\text{mol/L}\)) prevented the actions of isoproterenol to increase TDR and to induce TdP. Mexiletine 2 to 20 \(\mu\text{mol/L}\) abbreviated the APD\(_{90}\) of M cells more than that of epicardial and endocardial cells, thus diminishing TDR and the effect of isoproterenol to induce TdP.

Conclusions—This experimental model of LQT1 indicates that a deficiency of I\textsubscript{Ks} alone does not induce TdP but that the addition of β-adrenergic influence predisposes the myocardium to the development of TdP by increasing transmural dispersion of repolarization, most likely as a result of a large augmentation of residual I\textsubscript{Ks} in epicardial and endocardial cells but not in M cells, in which I\textsubscript{Ks} is intrinsically weak. Our data provide a mechanistic understanding of the cellular basis for the therapeutic actions of β-adrenergic blockers in LQT1 and suggest that sodium channel block with class IB antiarrhythmic agents may be effective in suppressing TdP in LQT1, as they are in LQT2 and LQT3, as well as in acquired (drug-induced) forms of the long-QT syndrome.

Key Words: long-QT syndrome ■ arrhythmia ■ KvLQT1 ■ chromanol 293b ■ isoproterenol

The long-QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the ECG and atypical polymorphic ventricular tachycardia that can lead to sudden cardiac death.\textsuperscript{1-6} It has long been appreciated that some forms of congenital and acquired LQTS are exquisitely sensitive to the activity of the sympathetic branch of the autonomic nervous system. An imbalance of sympathetic inputs to the heart was at one time thought to underlie congenital LQTS.\textsuperscript{1,6} Recent studies have shown that congenital LQTS is a primary electrical disease caused by mutations in specific ion channel genes.\textsuperscript{7}

Genetic linkage analysis has identified 4 forms of congenital LQTS caused by mutations in ion channel genes located on chromosomes 3, 7, 11, and 21.\textsuperscript{5-11} Chromosome 3–linked LQT3 is associated with a mutation in \(\alpha\)-subunit of the sodium channel in heart,\textsuperscript{8} whereas chromosome 7–linked LQT2 is associated with a mutation in \(HERG\), a gene that encodes for the channel that carries the rapidly activating delayed rectifier potassium current (I\textsubscript{Kr}).\textsuperscript{12} Chromosome 11–linked LQT1 is associated with a mutation in \(KvLQT1\) that encodes for the slowly activating delayed rectifier potassium current (I\textsubscript{Ks}),\textsuperscript{13,14} and chromosome 21–linked LQT5 is caused by a mutation in \(KCNE1\) (\(minK\)), whose product coassembles with that of \(KvLQT1\) to form the I\textsubscript{Ks} channel.\textsuperscript{11,13,14}

In the clinic, Moss and coworkers\textsuperscript{15} reported that patients with these ion channel defects often display different phenotypic T wave patterns in the ECG. LQT3 patients show distinctive late-appearing T waves, whereas LQT1 or LQT2 patients display broad-based, prolonged T waves or low-amplitude T waves, respectively.

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Among the 3 forms of congenital LQTS, cardiac events (cardiac arrhythmias and sudden cardiac death) are more likely to be associated with adrenergic factors (defined as either physical or emotional stress) in the LQT1 syndrome than in either the LQT2 or LQT3 syndrome. Moreover, β-blockers were reported to reduce cardiac events dramatically in LQT1 patients. The mechanisms responsible for these actions of the β-adrenergic system remain largely unknown.

Using an arterially perfused left ventricular wedge preparation, we recently developed models of LQT2 and LQT3 and showed that sodium channel block with mexiletine is effective in decreasing transmural dispersion of repolarization (TDR) and in suppressing TdP in both.

In the present study, we use this preparation to develop an experimental model of LQT1 in which we (1) elucidate the cellular basis of catecholamine-induced phenotypic appearance of broad-based T wave, increased TDR, and TdP and (2) examine the effects of rapid pacing as well as of β-adrenergic and sodium channel blockers to abbreviate the QT interval, diminish TDR, and prevent TdP.

### Methods

**Arterially Perfused Wedge of Canine Left Ventricle**

Dogs weighing 20 to 25 kg were anticoagulated with heparin and anesthetized with pentobarbital 30 to 35 mg/kg IV. The chest was opened via a left thoracotomy, and the heart was excised and placed in a cardioplegic solution consisting of cold (4°C) or room-temperature Tyrode’s solution containing 8.5 mmol/L [K+]o. Transmural wedges with dimensions of ~2x1.5x0.9 to 3x2x1.5 cm were dissected from the left ventricle. The tissue was cannulated via a small (diameter, ~100 μm) native branch of left anterior descending coronary artery and perfused with cardioplegic solution. Unperfused tissue, readily identified by its maintained red appearance (erythrocytes not washed away), was carefully removed with a razor blade. The preparation was then placed in a small tissue bath and arterially perfused with Tyrode’s solution bathing the preparation, 1.0 to 1.5 cm from the epicardial and endocardial surfaces, along the same vector as the transmembrane recordings (epicardial, positive pole). The electrical field of the preparation as a whole was measured by this technique. Thus, the ECG registration represents a pseudo-ECG of that part of the left ventricle. To differentiate it from local electrogram activity, we refer to it as an ECG in the text.

Transmembrane action potentials (APs) were recorded simultaneously from the epicardial, M, and endocardial sites with 3 or 4 separate intracellular floating microelectrodes (DC resistance, 10 to 20 MΩ; 2.7 mol/L KCl). Epicardial and endocardial APs were recorded from the epicardial and the endocardial surfaces of the preparations at positions approximating the transmural axis of the ECG recording. M cell APs were recorded from the site along the same axis at which AP duration (APD90) was homogeneous. *P<0.05, **P<0.0005 vs 0 μmol/L.

**Recordings of a Transmural ECG and Transmembrane Action Potentials**

The ventricular wedges were allowed to equilibrate until electrically stable, usually 1 hour, and stimulated with bipolar silver electrodes insulated except at the tips and applied to the endocardial surface. A transmural ECG was recorded with 3 mol/L KCl-agar electrodes (ID, 1.1 mm). The electrodes were placed in the Tyrode’s solution bathing the preparation, 1.0 to 1.5 cm from the epicardial and endocardial surfaces, along the same vector as the transmembrane recordings (epicardial, positive pole). The electrical field of the preparation as a whole was measured by this technique. Thus, the ECG registration represents a pseudo-ECG of that part of the left ventricle. To differentiate it from local electrogram activity, we refer to it as an ECG in the text.

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Amplified signals were digitized, stored on magnetic media and WORM-CD, and analyzed with Spike 2 (Cambridge Electronic Design).
Study Protocols

The $I_{Ks}$ blocker chromanol 293B 1 to 100 $\mu$mol/L was used to create a model that mimics the defect in $KV_{LQT1}$, which results in a reduced $I_{Ks}$, believed to underlie the congenital LQT1 syndrome. Isoproterenol 10 to 100 nmol/L was used to mimic increased $\beta$-adrenergic tone. The effects of $\beta$-adrenergic blockade were evaluated with propranolol 0.1, 0.3, 1, and 3 $\mu$mol/L and those of sodium channel blocker with mexiletine 2, 5, 10, and 20 $\mu$mol/L.

Control measurements were generally obtained after 1 hour of equilibration. The chromanol 293B data were collected for a period of up to 30 minutes starting 30 minutes after addition of the drug. Isoproterenol data in the absence and presence of chromanol 293B were collected within 10 minutes after addition of isoproterenol. Mexiletine and propranolol data were recorded after 30 minutes of exposure to each concentration of drug.

APD was measured at 90% repolarization ($APD_{90}$). TDR was defined as the difference between the longest and the shortest repolarization times (activation time + $APD_{90}$) of transmembrane APs recorded across the wall. The QT interval was defined as the time between QRS onset and the point at which the line of maximal downslope of the T wave crossed the baseline. Graphic correlation of transmembrane and ECG activity was achieved by dropping a dotted line from the point of full repolarization of the AP ($APD_{100}$, approximated by eye) to the ECG trace.

The development of spontaneous and programmed electrical stimulation (PES)–induced polymorphic ventricular tachycardia displaying characteristics of TdP was assessed in the presence of chromanol 293B 30 $\mu$mol/L or isoproterenol 10 to 100 nmol/L alone and after the combination of chromanol 293B and isoproterenol 50 to 100 nmol/L. PES-induced arrhythmias were evaluated with a single extrastimulus applied to the epicardium.

Statistics

Statistical analysis of the data was performed with a Student’s $t$ test for paired data or ANOVA coupled with Scheffe’s test, as appropriate. Data are expressed as mean ± SD values, except for those shown in the figures, which are expressed as mean ± SEM values.

Results

Dose-Dependent Effect of Chromanol 293B on QT Interval, APD, and TDR

Figure 1A illustrates the dose-dependent effect of chromanol 293B on transmembrane and ECG activity. Chromanol 293B, in concentrations ≥10 $\mu$mol/L, significantly prolonged the QT interval and $APD_{90}$ of the 3 cell types (Figure 1B). However, because the prolongation of $APD_{90}$ of the 3 cell types was homogeneous, chromanol 293B did not widen the T wave or significantly increase TDR (Figure 1C).

Rate Dependence of QT Interval, APD, and Dispersion of Repolarization

The rate-dependent changes in the QT interval were closely approximated by changes in the repolarization time of the M cell both under control conditions and after chromanol 293B, as illustrated in Figures 2 and 3. Chromanol 293B 30 $\mu$mol/L produced a steepening of the APD-rate relations and a significant prolongation of $APD_{90}$ and of the QT interval at all rates studied (Figures 2B, 3A, 3B, and 3C). TDR did not change significantly at any rate (Figures 2B and 3D) because...
of the effect of chromanol 293B to prolong the APD₉₀ of the 3 cell types homogeneously.

Influence of Isoproterenol on Phenotypic ECG Pattern, Transmembrane APD, TDR, and TdP

Figure 4 shows transmembrane activity recorded simultaneously from endocardial, M, and epicardial regions together with a transmural ECG in the absence and presence of chromanol 293B 30 μmol/L and in the presence of isoproterenol 100 nmol/L and chromanol 293B (basic cycle length [BCL], 2000 ms). In all cases, the peak of the T wave in the ECG was coincident with the repolarization of the epicardial cell, whereas the end of the T wave was coincident with the repolarization of the M region (deep subendocardium). Repolarization of the endocardial AP was intermediate between that of the M cell and epicardial cell. Thus, TDR across the ventricular wall was defined as the difference in the repolarization time between the M cell (longest AP) and epicardial cell (shortest AP). Once again, 30 μmol/L of chromanol 293B prolonged the APD of the 3 cell types and the QT interval, but it neither increased TDR nor widened the T wave (Figure 4B). Isoproterenol 10 to 100 nmol/L in the continued presence of chromanol 293B homogeneously prolonged the APD₉₀ of the M cell and the epicardial cell (234±14 to 298±22 ms; n=8; P<0.0005), resulting in no significant increase of TDR (43±6 to 47±7 ms; n=8). Isoproterenol in the continued presence of chromanol 293B significantly shortened the APD₉₀ of the epicardial cell (267±15 ms; n=8; P<0.0005 versus 293B) but not that of the M cell (350±19 ms; n=8) (Figure 5A), resulting in a significant increase of the TDR (75±9 ms; n=8; P<0.0005 versus 293B) (Figure 5B).

In 4 preparations, we examined the influence of isoproterenol 10, 50, and 100 nmol/L on transmembrane and ECG activity. Isoproterenol homogeneously abbreviated the APD₉₀ of the 3 cell types in a dose-dependent manner, thus abbreviating the QT interval with no major changes in TDR or width of the T wave.
Cells with a homogeneous prolongation of the QT interval and of APD <sub>90</sub>. In the continued presence of chromanol 293B, 0.1 to 1 μmol/L of propranolol exerted no significant effect, whereas the highest concentration (3 μmol/L) significantly abbreviated the APD <sub>90</sub> of the M cell, probably because of its effect to block the late sodium current (I<sub>Na</sub>), which is intrinsically larger in the M cell than in the epicardial cell.

**Effect of Propranolol on Repolarization Changes and TdP Induced by Isoproterenol**

Figure 7 illustrates the effect of propranolol 1 μmol/L to inhibit the influence of isoproterenol in a wedge preparation pretreated with chromanol 293B 30 μmol/L. Therapeutic concentrations of propranolol (0.5 to 1 μmol/L), which block β-adrenergic receptors in the heart with little or no block of I<sub>Na</sub>, completely prevented the influence of isoproterenol to increase TDR (Figures 7C and 7D).

The average data of 6 experiments are shown in Figure 8. Propranolol 1 μmol/L in the continued presence of chromanol 293B 30 μmol/L completely suppressed the influence of isoproterenol to shorten the APD <sub>90</sub> of the epicardial cell and to increase TDR (see Figures 4C, 5A, and 5B). Moreover, therapeutic concentrations of propranolol (0.5 to 1 μmol/L) totally suppressed the spontaneous as well as PES-induced TdP produced in the presence of isoproterenol and chromanol 293B.

### Dose-Dependent Effect of Propranolol on QT Interval, APD, and TDR

Table 2 summarizes the effects of mexiletine on QT interval, APD <sub>90</sub>, and TDR in the continued presence of chromanol 293B 30 μmol/L (BCL, 2000 ms; n=6). In the continued presence of chromanol 293B, 2 to 20 μmol/L of mexiletine dose-dependently abbreviated the QT interval and APD <sub>90</sub> of M cells more than those of epicardial cells, thus reducing TDR. Mexiletine 20 μmol/L reversed 70% of the effect of chromanol 293B to prolong the APD <sub>90</sub> of the M cell and the QT interval but only 45% of the effect of chromanol 293B to prolong the epicardial AP.

**Effect of Mexiletine on Repolarization Changes and TdP Induced by Isoproterenol**

Figure 9 illustrates the effect of mexiletine 20 μmol/L to inhibit the influence of isoproterenol on transmembrane and ECG activity in the continued presence of chromanol 293B 30 μmol/L. Mexiletine 10 to 20 μmol/L decreased TDR in

**TABLE 1. Dose-Dependent Effects of Propranolol on the QT Interval, APD<sub>90</sub>, and Dispersion of Repolarization in Perfused Wedge Preparation Pretreated With Chromanol 293B**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>293B 30 μmol/L</th>
<th>+Prop 0.1 μmol/L</th>
<th>+Prop 0.3 μmol/L</th>
<th>+Prop 1 μmol/L</th>
<th>+Prop 3 μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>306±9</td>
<td>384±21</td>
<td>383±21</td>
<td>381±22</td>
<td>371±20</td>
<td>347±13</td>
</tr>
<tr>
<td>APD&lt;sub&gt;90&lt;/sub&gt; (M cell)</td>
<td>284±13</td>
<td>357±25</td>
<td>355±24</td>
<td>354±25</td>
<td>344±26</td>
<td>320±17</td>
</tr>
<tr>
<td>APD&lt;sub&gt;90&lt;/sub&gt; (Epi)</td>
<td>226±17</td>
<td>296±34</td>
<td>294±33</td>
<td>294±33</td>
<td>289±33</td>
<td>273±25</td>
</tr>
<tr>
<td>Dispersion of RT</td>
<td>45±7</td>
<td>50±11</td>
<td>50±12</td>
<td>48±11</td>
<td>44±15</td>
<td>35±15</td>
</tr>
</tbody>
</table>

Epi indicates epicardial cell; Prop, propranolol; QT, QT interval; RT, repolarization time; and 293B, chromanol 293B.

*P<0.0005 vs control; †P<0.005 vs 293B.
the presence of chromanol 293B and prevented the influence of isoproterenol to increase TDR (Figures 9C and 9D).

Composite data of 6 experiments are shown in Figure 10. Mexiletine 20 μmol/L, in the continued presence of chromanol 293B 30 μmol/L abbreviated the M cell AP more than that of the epicardial cell, resulting in a significant decrease of TDR. In the continued presence of mexiletine, isoproterenol 50 to 100 mmol/L slightly abbreviated the APD₉₀ of the epicardial cell but not that of the M cell, resulting in a slight but statistically insignificant increase in TDR.

In concentrations of 10 to 20 μmol/L, mexiletine totally suppressed the spontaneous as well as PES-induced TdP provoked with isoproterenol.

Discussion

Catecholamine-Induced Broad-Based Long-QT and Increased Dispersion of Repolarization

Sympathetic stimulation or the administration of exogenous catecholamines is known to produce paradoxical QT prolongation and TdP, often associated with syncope or sudden cardiac death in patients with congenital LQTS.1–6 Cardiac arrhythmias and sudden death are more often associated with adrenergic factors, defined as physical and emotional stress, in patients with the LQT1 syndrome than in those with either the LQT2 or LQT3 syndrome.10 A mutation in KvLQT1, which coassembles with the product of KCNE1 to form the I₆ channel, has recently been shown to be responsible for the LQT1 syndrome.13,14 β-Adrenergic stimulation is known to increase ionic current through L-type calcium channels (I₉Ca), I₉K, and chloride channels [I(CaCl) and I(Ca-AMP)].15,20 A net increase of outward repolarizing current, due to a greater increase of I₆ and ICl versus Iᵣ, is usually encountered in response to adrenergic stimulation, and this is thought to underlie abbreviation of APD and QT interval under normal conditions. A smaller increase in I₆ (especially in the M region) could offset this balance and account for failure of adrenergic stimulation to abbreviate APD and QT interval in LQT1 patients.7,10,21,22

Our findings indicate that chromanol 293B, a relatively specific I₆ blocker,23 homogeneously prolongs the APD₉₀ of the 3 ventricular cell types, thus increasing the QT interval with little or no change in the width of the T wave or TDR. This response is different from that observed with all other APD-prolonging agents. Agents that block I₆, augment Iᵣ, or slow the inactivation of Iᵣ all produce a dramatic prolongation of the M-cell APD but a much more modest prolongation of the APD of epicardium and endocardium, presumably because of the presence of a strong net repolarizing current (strong I₆ and weak late Iᵣ) in the latter and weak net repolarizing current (weak I₆ and strong late Iᵣ) in the former. The homogeneous response to chromanol 293B is best explained by the presence of unequal levels of I₆ in the 3 cell types. Because epicardial and endocardial cells have a larger I₆ than M cells, the same percentage inhibition of I₆ in the 3 cell types would be expected to decrease total repolarizing current more in the epicardial and endocardial cells than the M cell, resulting in a greater prolongation of the APD of epicardial and endocardial cells. However, the smaller intrinsic repolarizing current of the M cell provides for a greater input (membrane) resistance during phases 2 and 3 of the AP. As a consequence, a smaller absolute decrease in I₆ can cause an APD prolongation in M cells comparable to that seen in epicardial and endocardial cells. Consistent with this reasoning, on a percentage basis, 293B-induced APD prolongation in epicardium and endocardium is greater than in the M cell.
In the continued presence of chromanol 293B, β-adrenergic stimulation with isoproterenol abbreviates the APD$_{90}$ of epicardial and endocardial cells but not that of the M cell, resulting in an accentuated TDR and a broad-based T wave, consistent with the phenotypic appearance of the ECG in patients afflicted with the LQT1 syndrome. The differential response to isoproterenol is probably the result of intrinsic differences in $I_{Kr}$ among the 3 cell types. A large augmentation of residual $I_{Kr}$ would be expected in epicardial and endocardial cells but not in M cells, in which $I_{Kr}$ is intrinsically weak. The weaker endocardial response is most likely due to the strong electrotonic influence of the M cells, which reside in the deep subendocardium in this part of the left ventricular wall. When studied as isolated strips, epicardial and endocardial APs prolonged by chromanol 293B display a marked abbreviation in response to isoproterenol, whereas the M-cell preparations usually exhibit a prolongation of APD within the first few seconds of exposure to isoproterenol (unpublished data).

Our data indicate the lack of an arrhythmogenic substrate when $I_{Kr}$ is diminished in the absence of β-adrenergic influence. Because sympathetic tone is always present under normal physiological conditions, decreased levels of $I_{Kr}$ may be arrhythmogenic under conditions in which the sympathetic system has not been pharmacologically or surgically disabled. The concordance of our results in the wedge with the phenotypic ECG and pharmacological manifestations of LQT1 observed in patients suggests that chromanol 293B is a reasonable surrogate for the LQT1 syndrome.

**Catecholamine-Induced TdP**

TdP is an atypical polymorphic ventricular tachycardia most often associated with QT prolongation in both the congenital and acquired forms of LQTS. Although the precise mechanism of TdP has not been established, several experimental and clinical observations using monophasic AP recordings and perfused-wedge studies from our group suggest a role for early afterdepolarization (EAD)–induced triggered activity in the genesis of TdP. Recent in vivo studies from El-Sherif et al and perfused-wedge studies from our group present evidence in support of the hypothesis that an EAD-induced triggered response initiates TdP but that the arrhythmia is maintained by a reentrant mechanism. Our data, showing induction of TdP only in the presence of chromanol 293B and isoproterenol under conditions in which TDR is increased, provide further support for reentry as the basis for the maintenance of TdP. Conversely, several experimental studies have suggested that inward current through $I_{Kr}$ channels or through sodium-calcium exchange contributes to development of EADs. These mechanisms are thought to contribute to the effect of β-adrenergic agonists to induce EADs and triggered activity in M cells and Purkinje fibers, in which repolarizing currents are reduced. Thus, sympathetic stimulation may create the substrate for EAD-induced triggered activity as well as the substrate for reentry in the LQT1 syndrome.

**Effect of Rapid Pacing on QT Interval, APD, and TDR**

The present study shows a reduction of TDR as a function of rate and a steeper APD-rate relation for APD$_{90}$ and QT interval under LQT1 conditions compared with control. Unlike $I_{Kr}$ block, whose APD-prolonging effects are abolished at fast rates, $I_{Kr}$ block with 293B prolongs APD$_{90}$ and QT even at BCLs as short as 300 ms (Figures 2 and 3). The

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**Figure 9.** Effect of mexiletine (Mex) 20 μmol/L to suppress influence of isoproterenol (Iso) 100 nmol/L on APD and QT interval in perfused-wedge preparations treated with chromanol 293B 30 μmol/L. Each trace shows superimposed APs recorded simultaneously from M and epicardial (Epi) cells together with a transmural ECG at a BCL of 2000 ms. A, Control. B, Chromanol 293B. C, Mexiletine preferentially abbreviated M cell AP more than that of epicardial cell, resulting in a decrease of TDR (32 ms). D, Mexiletine suppressed marked influence of isoproterenol to increase TDR (38 ms).
protective effect of pacing in LQTS has been documented in other experimental models as well as in the clinic.\textsuperscript{18,31,32}

**Effect of Propranolol on Repolarization and TdP**

\(\beta\)-Blockers are widely reported to reduce the incidence of syncope and sudden death in patients with congenital LQTS.\textsuperscript{4} Consistent with reports of a high sensitivity of patients with the LQT1 syndrome to adrenergic stimulation, greater than those with either LQT2 or LQT3 syndrome,\textsuperscript{16} \(\beta\)-blockers have been shown to reduce cardiac events very effectively in LQT1 patients.\textsuperscript{17} Priori et al\textsuperscript{33} reported that in patients with the Romano-Ward form of LQTS, cardiac events were reduced more in patients in whom \(\beta\)-blockers caused a large decrease in corrected QT (QTc) dispersion. In contrast, other clinical studies have shown that \(\beta\)-blockers modified neither QTc interval nor QTc dispersion as measured with a 12-lead ECG\textsuperscript{34} or an 87-lead body surface mapping system in the LQTS patients.\textsuperscript{35} Our finding of little or no effect of therapeutic levels of propranolol (0.1 to 1 \(\mu\)mol/L) on QTc dispersion was in agreement with the latter observations. Nevertheless, the effects of isoproterenol to increase TDR and to reduce the action of isoproterenol to produce spontaneous as well as PES-induced TdP were completely inhibited by propranolol in therapeutic concentrations. Our data point to a diminution of TDR during normal sympathetic tone or its actions to prevent accentuation of TDR after a strong sympathetic discharge.

**Effect of Mexiletine on Repolarization and TdP**

Recent preliminary clinical studies suggested that sodium channel block with mexiletine is more effective in abbreviating the QT interval in LQ3 patients (those manifesting the sodium channel defect) than in either LQT1 or LQT2 patients (those with the \(I_{K}\) defect).\textsuperscript{31,38} A significant mexiletine-induced abbreviation of QT was observed in <10% of LQT1 patients.\textsuperscript{38} However, studies using the arterially perfused wedge have shown that although mexiletine is more effective in abbreviating the QT interval in the LQT3 than in the LQT2 model, the sodium channel blocker reduces TDR and prevents the development of TdP equally in the 2 models.\textsuperscript{18} The present study of the LQT1 model shows the effect of mexiletine to reduce the QT interval and TDR in the absence of isoproterenol and to reduce the action of isoproterenol to accentuate TDR and induce TdP. Our results suggest that sodium channel block with mexiletine in combination with \(\beta\)-blockade warrants further consideration as a therapeutic approach in the treatment of the LQT1 syndrome.

**Limitations of the Study**

Our interpretations of the data are based on the assumption that the activity recorded from the cut surface of the perfused-wedge preparation is representative of cells within the respective layers of the wall throughout the wedge. Such validation was provided in 2 previous studies that used the perfused-wedge preparation.\textsuperscript{18,37} The extent to which chromanol 293B–induced inhibition of \(I_{K}\) mimics the \(K_{V,LQT1}\) defect responsible for the LQT1 syndrome is difficult to quantify, because the current density of \(I_{K}\) is intrinsically heterogeneous in the 3 cell types. Our data demonstrate the ability of the model to closely mimic the ECG and pharmacological features of the LQT1 syndrome, including a prolonged QT interval, broad-based T waves, a modestly steep QT-rate relation, and exceptional sensitivity to \(\beta\)-adrenergic influences. We believe that these qualitative similarities validate chromanol 293B as a surrogate for LQT1.

Our LQT1 model is less than physiological with respect to the manner in which sympathetic influences are examined. An imbalance between left and right stellate inputs to the heart was first suggested to underlie LQTS in 1975.\textsuperscript{1} The sympathetic-imbalance hypothesis as a primary cause lost ground when genetic linkage analysis uncovered 4 gene mutations responsible for ion channel defects. The role of the sympathetic system remained largely unexplained. The present study advances our understanding of the action of \(\beta\)-adrenergic influences to amplify transmural dispersion of repolarization. However, perfusion of the wedge preparations with isoproterenol causes homogeneous stimulation of \(\beta_{1}\) receptors only and does not take into account differences in the distribution of left and right sympathetic stellate inputs to the heart or the possibility that a pathophysiological sympathetic imbalance may further amplify transmural and interventricular dispersion of repolarization. This disclaimer notwithstanding, the available data suggest the hypothesis that differences in the distribution and characteristics of M cells in right versus left ventricle coupled with physiological differences in right versus left sympathetic innervation of the heart can explain the preeminent role of the left stellate in LQTS. This hypothesis remains to be tested.
Cellular Basis for the ECG in LQT1

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