Improvement of Repolarization Abnormalities by a K⁺ Channel Opener in the LQT1 Form of Congenital Long-QT Syndrome

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Background—This study used monophasic action potential (MAP) to examine the effect of nicorandil, a K⁺ channel opener, on repolarization abnormalities induced by epinephrine in the LQT1 form of congenital long-QT syndrome in which the KvLQT1 mutation underlies the defect in the channel responsible for the slowly activating component of the delayed rectifier potassium current.

Methods and Results—MAPs were recorded simultaneously from two or three sites on the right ventricular and left ventricular endocardium in 6 patients with a congenital form of LQT1 syndrome with KvLQT1 defect (17 sites) and 8 control patients (24 sites). In LQT1 patients, epinephrine infusion prolonged the QT interval and 90% MAP duration (MAPD₉₀) and increased the dispersion of MAPD₉₀. Epinephrine also induced early afterdepolarizations (EADs) as well as ventricular premature complexes (VPCs) in 2 of the 6 patients. Nicorandil during epinephrine infusion abbreviated the QT interval and MAPD₉₀, decreased the dispersion of MAPD₉₀, and abolished the EADs as well as the VPCs in 1 patient. Addition of propranolol completely reversed the effect of epinephrine in prolonging the QT interval and MAPD₉₀ and increasing the dispersion and eliminated the EADs and VPCs in another patient. In control patients, the effect of epinephrine and that of additional nicorandil and propranolol on repolarization parameters were much less than in the LQT1 patients.

Conclusions—Our results suggest that nicorandil, a K⁺ channel opener, improves repolarization abnormalities in the LQT1 form of congenital long-QT syndrome with KvLQT1 defect. (Circulation. 1998;97:1581-1588.)

Key Words: long-QT syndrome • potassium • receptors, adrenergic, beta • depolarizing • action potentials

Recent genetic linkage analyses have identified three forms of congenital LQTS caused by mutations in ion channel genes located on chromosomes 3, 7, and 11. Chromosome 3-linked LQT3 is associated with mutations in SCN5A, a gene that is related to inactivation of the sodium channel, whereas chromosome 11-linked LQT1 and chromosome 7-linked LQT2 are associated with mutations in KvLQT1 and HERG that are linked to defects in the channel responsible for the Iᵦᵥ, and the Iᵦ, respectively. The direct link of mutated genes to dysfunction of ion channels appears to lend some support to genetically defined therapy of congenital forms of LQTS. Schwartz and coworkers showed that sodium channel block with mexiletine is much more effective in abbreviating QT interval in LQT3 patients (those manifesting the sodium channel defect) than in LQT2 patients. Exogenously administered potassium has been reported to correct repolarization abnormalities in LQT2 patients (those with the potassium channel defect).

Thus, we hypothesized that K⁺ channel openers could increase outward potassium current to improve repolarization abnormalities in a congenital form of chromosome 11-linked LQT1 syndrome in which the KvLQT1 mutation is believed to underlie the defect in the channel responsible for Iᵦ. To test this hypothesis, we recorded MAP and examined the effect of intravenous nicorandil, a K⁺ channel opener, on repolarization abnormalities induced by epinephrine infusion in the LQT1 form of congenital LQTS.

Methods

Subjects
The study population consisted of 6 patients with the congenital form of chromosome 11-linked LQT1 syndrome and 8 control patients. All 6 patients with the congenital form of LQTS were genotyped as chromosome 11-linked LQT1 syndrome with KvLQT1 defect; these included 3 female and 3 male patients 6 to 42 years old (mean, 24±15 years) (Table 1). Three patients (patients 1, 2, and 3) were family members. The other 3 patients (patients 4, 5, and 6) had family members with the congenital form of LQTS, which was defined according to the new diagnostic criteria of Schwartz et al. Five patients had a history of stress-induced syncope, and TdP was documented in 4 patients. One patient had occasional palpitations.

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Control patients

TABLE 1. Clinical Characteristics of 6 LQT1 Patients and 8 Control Patients

<table>
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<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Family Member</th>
<th>Symptoms</th>
<th>ECG Findings</th>
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<tr>
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SCL indicates sinus cycle length; LQT1, LQT1 form of congenital long-QT syndrome; ConWPW, concealed Wolff-Parkinson-White syndrome; +, present; and -, absent.
Figure 1. Twelve-lead ECG demonstrating broad-based prolonged T-wave pattern and marked QT prolongation (QTc = 560 ms) in patient with congenital form of LQT1 syndrome with KvLQT1 defect (patient 1).

Sinus Cycle Length and Systolic Blood Pressure

Epinephrine significantly shortened the sinus cycle length both in patients with congenital LQT1 syndrome and in control patients (P < 0.0005 versus control state). Injection of nicorandil during epinephrine infusion did not change the sinus cycle length in patients of either group, whereas addition of propranolol during epinephrine infusion significantly prolonged it (P < 0.0005 versus nicorandil). Epinephrine significantly increased the systolic blood pressure during constant atrial pacing (CL, 600 ms) in patients of both groups (LQT1 patients, P < 0.001; control patients, P < 0.05 versus control state). Neither nicorandil nor addition of propranolol during epinephrine infusion changed the systolic blood pressure in patients of either group (Table 2).

MAPD90

The MAPD90 was significantly longer in patients with congenital LQT1 syndrome (n = 17) than in control patients (n = 24) during constant atrial pacing at the control state (314 ± 35 versus 243 ± 12 ms; P < 0.0005). In LQT1 patients, epinephrine markedly prolonged the MAPD90 to 347 ± 48 ms (P < 0.0005 versus control state) (Figs 2B, 3B, and 4A). Injection of nicorandil during epinephrine infusion significantly abbreviated the MAPD90 to 328 ± 38 ms (P < 0.005 versus epinephrine) (Figs 2C, 3C, and 4A). Addition of propranolol during epinephrine infusion completely reversed the effect of epinephrine in prolonging the MAPD90 (315 ± 32 ms, P < 0.05 versus nicorandil) (Figs 2D, 3D, and 4A). In control patients, epinephrine also prolonged the MAPD90 to 249 ± 14 ms (P < 0.0005 versus control state). However, the prolongation of MAPD90 in control patients was much smaller than that in LQT1 patients (difference in the mean MAPD90 before and after epinephrine, 33 versus 6 ms). Injection of nicorandil and addition of propranolol during epinephrine infusion did not change the MAPD90 in control patients (nicorandil, 248 ± 13 ms; propranolol, 246 ± 13 ms) (Fig 4B).
90 recordings show dispersion of MAPD decreased dispersion of MAPDgo, although EAD was not eliminated simultaneously from right ventricular outflow tract (RVOT), MAP recording show MAPDgo, and those at bottom of MAP recordings show reversed effects of epinephrine to control level. Numbers in each MAP recording show MAPDgo in all sites, and increased dispersion of MAPDgo. C, Nicorandil abbreviated QT interval and MAPD90 in all sites, and decreased dispersion of MAPD90.

**Dispersion of MAPD90**

There was no significant difference in the dispersion of MAPD90 between patients with congenital LQT1 syndrome (n=6) and control patients (n=8) in the control state (26±6 ms). In LQT1 patients, epinephrine increased the dispersion of MAPD90 to 45±13 ms (P<.01 versus control state) (Figs 2B, 3B, and 5A). Injection of nicorandil during epinephrine infusion decreased the dispersion to 26±7 ms (P<.01 versus epinephrine) (Figs 2C, 3C, and 5A). Addition of propranolol during epinephrine infusion further decreased it to 17±8 ms, although this difference did not reach statistical significance (Figs 2D, 3D, and 5A). In control patients, the dispersion of MAPD90 did not change during the entire protocol (epinephrine, 24±6 ms; nicorandil, 23±5 ms; propranolol, 23±5 ms) (Fig 5B).

**T-Wave Morphology and QT Interval**

The QT interval was significantly longer in patients with the congenital form of LQT1 syndrome (n=6) than in control patients (n=8) during constant atrial pacing in the control state (397±23 versus 323±8 ms; P<.0005). In LQT1 patients, epinephrine increased the peak or the late component of T waves in precordial leads and markedly prolonged the QT interval to 443±40 ms (P<.001 versus control state) (Figs 2B, 3B, and 6A). Injection of nicorandil during epinephrine infusion slightly decreased the amplitude of the T wave and shortened the QT interval to 420±29 ms, although this difference did not reach statistical significance (P=.09 versus epinephrine) (Figs 2C, 3C, and 6A). Addition of propranolol during epinephrine infusion further decreased the T-wave amplitude and completely reversed the effect of epinephrine in prolonging the QT interval (394±18 ms, P=.1 versus nicorandil) (Figs 2D, 3D, and 6A). In control patients, epinephrine also prolonged the QT interval to 335±8 ms (P<.0005 versus control state). However, the prolongation of the QT interval in control patients was much smaller than that during epinephrine during epinephrine.

<table>
<thead>
<tr>
<th>Table 2. Changes of SCL and SBP During Atrial Pacing (600 ms)</th>
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<td>Congenital LQT1 patients, n</td>
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<td>Control patients, n</td>
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<tr>
<td>SCL, ms</td>
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<td>SBP, mm Hg</td>
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</table>

SCL indicates sinus cycle length; SBP, systolic blood pressure; and LQT1, LQT1 form of congenital long-QT syndrome.

* P<.0005; † P<.001; ‡ P<.05 vs control; § P<.0005 vs nicorandil during epinephrine.
in LQT1 patients (difference in the mean QT interval before and after epinephrine, 46 versus 12 ms), and the T-wave morphology was not changed in control patients as in LQT1 patients. Injection of nicorandil and addition of propranolol during epinephrine infusion did not change the T-wave morphology or the QT interval in control patients (nicorandil, 334±5 ms; propranolol, 328±9 ms) (Fig 6B).

**Early Afterdepolarizations**

In the control state, no EADs were recorded in any patients with congenital LQT1 syndrome. Epinephrine induced EADs in 2 of the 6 patients with LQT1 syndrome (two recording sites). The EADs were recorded at the right ventricular outflow tract in patient 1 (Fig 2B) and at the LV lateral wall in patient 6 (Fig 3B). Injection of nicorandil during epinephrine infusion abolished the EADs in patient 6, whereas addition of propranolol during epinephrine infusion eliminated the EADs in patient 1 (Fig 2D). The 2 patients in whom EADs were recorded had longer MAPD$_{90}$ during both the control state and epinephrine infusion and showed greater response to nicorandil. Recordings of EADs were stable during the same protocol, and the shape and amplitude of EADs were constant during constant atrial pacing (constant RR interval) in the LQT1 syndrome. Moreover, the amplitude of EADs was bradycardia-dependent and increased after a long preceding RR interval after atrial pacing. These characteristics of EADs were consistent with those of experimentally induced EADs.

No EADs were recorded during the entire protocol in any control patients.

**Ventricular Arrhythmias**

In the control state, there were no ventricular arrhythmias in any patients with congenital LQT1 syndrome. Epinephrine induced VPCs in 2 patients with LQT1 syndrome in whom EADs were induced by epinephrine. The morphology of the VPCs showed right bundle-branch block pattern with right-axis deviation in patient 1 and right bundle-branch block pattern with left-axis deviation in patient 6, suggesting that the VPCs originated near the LV outflow tract and the LV inferior wall, respectively. Injection of nicorandil during epinephrine infusion abolished the VPCs as well as the EADs in patient 6, whereas addition of propranolol during epinephrine infusion eliminated the VPCs and EADs in patient 1. There were no VPCs during the entire protocol in any control patients.

**Discussion**

Catecholamine-Induced Repolarization Abnormalities and Effects of K+ Channel Openers and β-Blockers in Congenital Form of LQT1 Syndrome

Sympathetic stimulation or catecholamines are well known to produce paradoxical QT prolongation and TdP, which are often linked to syncope or sudden cardiac death in patients with congenital LQTS. Among three forms of the congenital LQTS caused by ion channel mutations, cardiac events (cardiac arrhythmias and sudden cardiac death) are more
likely to be associated with adrenergic factors (defined as physical and emotional stress) in the LQT1 syndrome than in either the LQT2 or LQT3 syndrome.\textsuperscript{23-25} Commensurate with this, β-blockers were reported to reduce cardiac events dramatically in LQT1 syndrome.\textsuperscript{26} Recent genetic linkage analysis studies have shown that a mutation in \textit{KvLQT1}, which is responsible for LQT1 syndrome, altered the effect of the coexpression of \textit{minK} and \textit{KvLQT1}, which resulted in an impairment in the \( I_{Ks} \) current.\textsuperscript{15} β-Adrenergic stimulation increases inward current through \( I_{Ca-L} \) and outward repolarizing \( I_{Ks} \) and \( I_{Cl} \) current.\textsuperscript{27,28} A net increase of outward repolarizing current, because of a greater increase in \( I_{Ks} \) and \( I_{Cl} \) than in \( I_{Ca-L} \), is usually encountered in response to adrenergic stimulation, and this mechanism is thought to be responsible for the abbreviation of APD and QT interval under normal conditions. Therefore, a lack of increase in \( I_{Ks} \) could offset this balance and account for failure of adrenergic stimulation to abbreviate APD and QT interval appropriately in LQT1 syndrome.\textsuperscript{29} Several experimental studies have suggested that inward current through \( I_{Ca-L} \)\textsuperscript{30} or through sodium-calcium exchange\textsuperscript{31} was responsible for the development of EADs. Thus, adrenergic stimulation may easily create the substrate for EAD-induced triggered activity in LQT1 syndrome in which APD remains prolonged.\textsuperscript{30}

In the present study, epinephrine prolonged the MAPD\textsubscript{90} and QT interval and increased the dispersion of MAPD\textsubscript{90} much more in patients with congenital LQT1 syndrome than in control patients. Epinephrine also induced EADs and VPCs in 2 of the 6 patients with LQT1 syndrome but not in control patients. In the continued presence of epinephrine, nicorandil abbreviated the MAPD\textsubscript{90} and QT interval, decreased the dispersion of MAPD\textsubscript{90}, and abolished EADs as well as VPCs in 1 of the 2 patients.

Nicorandil, which increases outward potassium current through \( I_{KATP} \), was found to shorten APD and to suppress EADs induced by cesium chloride in \textit{vitro}\textsuperscript{32,33} and in \textit{vivo}\textsuperscript{34} experimental studies. Two other \( I_{KATP} \) openers, pinacidil and cromakalim, were also reported to effectively suppress EADs and ventricular arrhythmias in the long-QT models produced by cesium chloride,\textsuperscript{35} clofilium,\textsuperscript{36} or Bay K 8644.\textsuperscript{37} Recently, several groups used MAP recordings and showed the effect of nicorandil in decreasing MAP duration and abolishing EADs.\textsuperscript{38-40} Our data as well as those in the previous studies suggest that \( I_{KATP} \) opensers increase net outward repolarizing current even in case of a defect of \( I_{Ks} \) current during adrenergic stimulation to improve repolarization abnormalities in the congenital form of LQT1 syndrome with \textit{KvLQT1} defect.

Propranolol in addition to nicorandil completely reversed the effect of epinephrine in prolonging the MAPD\textsubscript{90} and QT interval, increasing the dispersion of MAPD\textsubscript{90}, and inducing EADs as well as VPCs. The effect of β-blockers is likely to be mediated by decreasing \( I_{Ca-L} \) as well as preventing catecholamine from binding to β-adrenergic receptors and is different from that of \( I_{KATP} \) openers. Moreover, because the effect of intravenous injection of nicorandil is relatively short (half-life, 5 to 10 minutes), the effect of nicorandil was likely to be very small at the time that the effect of propranolol was examined. These results support the dramatic effect of β-blockers in reducing cardiac events in patients with the congenital form of LQT1 syndrome.

**Mechanism of Long QT and TdP and Effect of K\textsuperscript{+} Channel Openers**

TdP is an atypical polymorphic ventricular tachycardia most often associated with QT prolongation in both congenital and acquired forms of LQTS. Several experimental\textsuperscript{41-42} and clinical observations using MAPs\textsuperscript{12-14,16,34-48} suggested a significant role for EAD-induced triggered activity in the genesis of TdP. El-Sherif et al\textsuperscript{49} recently used high-resolution tridimensional isochronal maps of activation and repolarization patterns and showed that the initial beat of the TdP appeared to arise from a focal subendocardial site, whereas subsequent beats were due mainly to reentrant excitation. Antzelevitch and coworkers\textsuperscript{44,46} used isolated arterially perfused canine LV wedge preparations and demonstrated the important role of transmural heterogeneity of action potentials in the induction of TdP, suggesting intramural reentry as the basis for the maintenance of TdP. Using MAP recordings, Shimizu et al\textsuperscript{40} demonstrated that the initiating beats (VPCs) of TdP were closely related to triggered activity arising from EADs in patients with the congenital form of LQTS.

In the present study, epinephrine infusion induced EADs as well as VPCs in 2 of 6 patients with LQT1 syndrome. The recording site of the EADs (right ventricular outflow tract and LV lateral wall, respectively) was relatively close to the origin of the VPCs (LV outflow tract and LV inferior wall, respectively), which was estimated by the morphology of the VPCs, although a direct relationship between the EADs and the VPCs could not be demonstrated. Moreover, nicorandil simultaneously eliminated the EADs and VPCs in 1 of the 2 patients (patient 6), whereas additional propranolol did the same in another (patient 1). In addition, both nicorandil and propranolol decreased the dispersion of MAPD\textsubscript{90}. These results suggest that the epinephrine-induced VPCs were related to the EADs. Our data also suggest that the effect of K\textsuperscript{+} channel openers and β-blockers on ventricular arrhythmias may be due to (1) suppression of EAD-induced triggered activity responsible for the spontaneous premature beats that precipitate TdP and/or (2) reduction of dispersion of repolarization, which leads to elimination of the substrate for reentry.

**Study Limitations**

There are several limitations in the present study. The first is the possibility that the EADs recorded in the MAPs represent artifacts. A recent computer simulation study suggested that apparent EADs recorded by the MAPs may reflect marked prolongation of APD in M cells with normal APD in the endocardium, in the absence of EADs in either tissue.\textsuperscript{47} However, recordings of prolonged MAP duration including EADs reflect the existence of prolonged APD at a region near the MAP electrode, so they enable us at least to evaluate the increased dispersion of repolarization. Second, the present study demonstrated the effects of intravenous nicorandil in improving repolarization abnormalities in the congenital form of LQT1 syndrome. Further studies are needed to decide the efficacy of chronic oral therapy of K\textsuperscript{+} channel openers in
suppressing TdP and sudden cardiac death in the long-QT syndrome. Third, we were not able to examine the effect of nicorandil in the presence of propranolol. Because β-blockers are the first line of therapy, especially in the LQTI syndrome, it is also important to know whether nicorandil offers any effects in addition to those of propranolol.

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References


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