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 and 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 I_k1.5, and the I_Ks, 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 I_Ks. 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) had 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.
They had a mean QTc interval of 517±26 ms\(^2\) (range, 480 to 560 ms\(^2\)), which was unrelated to antiarrhythmic agents, electrolyte abnormalities, or any other causes leading to QT prolongation. All 6 patients had broad-based prolonged T waves consistent with the ECG pattern reported by Moss et al.\(^6\) in LQT1 syndrome (Fig 1).

Eight control patients with concealed Wolff-Parkinson-White syndrome were also studied after successful radiofrequency catheter ablation for accessory atrioventricular connections. These were 2 female and 6 male patients 15 to 46 years old (mean, 35±10 years) with normal QT intervals (QTc, 416±12 ms\(^2\)) (Table 1).

### MAP Recordings

MAPs were recorded simultaneously from two or three sites on the right ventricular and LV endocardium in each patient by the contact electrode technique described previously (a total of 17 recording sites in 6 patients with congenital LQT1 syndrome; a total of 24 recording sites in 6 control patients).\(^{11,12}\) MAP signals amplified and filtered at a frequency of 0.05 to 400 Hz, 12 surface ECG leads, and radial artery pressure were recorded simultaneously by a computerized multichannel system (EPLab, Quinton Electrophysiology Corp), which allowed 32 simultaneous tracings to be printed on a strip-chart recorder (paper speed from 25 to 200 mm/s) (Hewlett Packard, Laser Jet III).\(^7\) Data were stored on optical disks for subsequent reproduction. MAPs were obtained during both sinus rhythm and constant atrial pacing at a CL of 600 ms after placement of the catheter electrode in a position providing continuous recordings with a stable amplitude, smooth configuration, and isopotential diastolic baseline (phase 4). Once the contact catheter was stabilized, MAPs could be recorded continuously from the same endocardial site for long periods without additional catheter manipulation.

EADs were defined as depolarizing afterpotentials that interrupted or delayed repolarization of the action potential.\(^13\) MAPD\(_{90}\) was determined, which included EADs if present. The dispersion of MAPD\(_{90}\) was defined as the difference between the longest and the shortest MAPD\(_{90}\) in each patient. Because the MAP recordings were obtained simultaneously from the right and left ventricles in all patients, the dispersion of MAPD\(_{90}\) included both the right ventricular and LV values. The QT interval was defined as the time between QRS onset and the point at which the line of maximal downslope of
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).

Protocol
Constant right atrial pacing (CL, 600 ms) was performed with 2-ms rectangular stimuli at twice diastolic threshold delivered from a programmable stimulator (SEC-3102, Nihon Kohden Inc.). Recordings of MAP in the control state were obtained during constant atrial pacing for at least 3 minutes until the MAP duration reached a new steady state. The mean of MAPD90 and QT interval of more than three consecutive beats during constant atrial pacing were used for analysis.

Epinephrine Infusion
After the MAP recordings at the control state, epinephrine was infused at a constant rate of 0.1 μg · kg⁻¹ · min⁻¹ in patients of both groups. After a steady state was achieved, MAP recordings during constant atrial pacing (CL, 600 ms) were obtained as described above. The ability of epinephrine infusion to induce ventricular arrhythmias spontaneously was assessed during sinus rhythm.

Noricandil Injection
Next, noricandil (0.1 mg/kg) was injected for 3 minutes during continuous epinephrine infusion in patients of both groups. MAP recordings during constant atrial pacing (CL, 600 ms) were obtained 5 minutes after the completion of noricandil injection, and the effect of noricandil on MAP parameters was investigated. The effect of noricandil in suppressing any ventricular arrhythmias induced by epinephrine was examined.

Propranolol Injection
In patients of both groups, propranolol (0.1 mg/kg) was injected for 5 minutes during continuous epinephrine infusion ~20 minutes after the completion of noricandil injection. MAP recordings during constant atrial pacing (CL 600 ms) were obtained 5 minutes after the completion of propranolol injection. The effects of propranolol on MAP parameters and in suppressing any ventricular arrhythmias was examined.

Statistical Analysis
Data are reported as mean±SD. Repeated-measures ANOVA followed by Scheffe's test was used to compare measurements made before and after serial drug administration. Student's t test for unpaired data was used to compare differences between LQT1 patients and control patients. A value of P<.05 was regarded as significant.

Results
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<.0005 versus control state). Injection of noricandil 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<.0005 versus noricandil). Epinephrine significantly increased the systolic blood pressure during constant atrial pacing (CL, 600 ms) in patients of both groups (LQT1 patients, P<.001; control patients, P<.05 versus control state). Neither noricandil nor addition of propranolol during epinephrine infusion changed theystolic 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<.0005). In LQT1 patients, epinephrine markedly prolonged the MAPD90 to 347±48 ms (P<.0005 versus control state) (Figs 2B, 3B, and 4A). Injection of noricandil during epinephrine infusion significantly abbreviated the MAPD90 to 328±38 ms (P<.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<.05 versus noricandil) (Figs 2D, 3D, and 4A). In control patients, epinephrine also prolonged the MAPD90 to 249±14 ms (P<.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 noricandil and addition of propranolol during epinephrine infusion did not change the MAPD90 in control patients (noricandil, 248±13 ms; propranolol, 246±13 ms) (Fig 4B).
Dispersion of MAPD<sub>90</sub>

There was no significant difference in the dispersion of MAPD<sub>90</sub> between patients with congenital LQT1 syndrome (n=6) and control patients (n=8) in the control state (26±8 versus 26±6 ms). In LQT1 patients, epinephrine increased the dispersion of MAPD<sub>90</sub> 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 MAPD<sub>90</sub> 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

### Table 2. Changes of SCL and SBP During Atrial Pacing (600 ms)

<table>
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<tr>
<th>Condition</th>
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<th>Epinephrine</th>
<th>Nicorandil</th>
<th>Propranolol</th>
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<td>SCL, ms</td>
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<td>672±74&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>960±75&lt;sup&gt;§&lt;/sup&gt;</td>
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<td>SCL, ms</td>
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<td>145±19‡</td>
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SCL indicates sinus cycle length; SBP, systolic blood pressure; and LQT1, LQT1 form of congenital long-QT syndrome.

<sup>*</sup> P<.0005; † P<.001; ‡ P<.05 vs control; § P<.0005 vs nicorandil during epinephrine.

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**Figure 2.** Recordings of MAP during constant atrial pacing (CL, 600 ms) in control state, during epinephrine infusion (0.1 μg·kg<sup>-1</sup>·min<sup>-1</sup>), after nicorandil injection (0.1 mg/kg) during epinephrine, and after addition of propranolol injection (0.1 mg/kg) during epinephrine in patient with congenital form of LQT1 syndrome (patient 1). Shown are ECG leads V<sub>5</sub>, V<sub>6</sub>, and MAP recording simultaneously from right ventricular outflow tract (RVOT), RV anterior wall (RVant), and LV lateral wall (LVIat). B. Epinephrine induced EAD in RVOT MAP (arrow), prolonged QT interval and MAPD<sub>90</sub> in all sites, and increased dispersion of MAPD<sub>90</sub>. C. Nicorandil abbreviated QT interval and MAPD<sub>90</sub> in all sites, and decreased dispersion of MAPD<sub>90</sub>. D. Addition of propranolol abolished EAD and completely reversed effects of epinephrine to control level. Numbers in each MAP recording show dispersion of MAPD<sub>90</sub>. Those at bottom of MAP recordings show dispersion of MAPD<sub>90</sub>.

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**Figure 3.** Recordings of MAP during constant atrial pacing (CL, 600 ms) in control state, during epinephrine infusion (0.1 μg·kg<sup>-1</sup>·min<sup>-1</sup>), after nicorandil injection (0.1 mg/kg) during epinephrine, and after addition of propranolol injection (0.1 mg/kg) during epinephrine in patient with congenital form of LQT1 syndrome (patient 6). Shown are ECG leads V<sub>5</sub>, V<sub>6</sub>, and MAP recording simultaneously from right ventricular outflow tract (RVOT), RV septum (RVsep), and LV lateral wall (LVIat). B. Epinephrine induced EAD in LVIat MAP (arrow), prolonged QT interval and MAPD<sub>90</sub> in all sites, and increased dispersion of MAPD<sub>90</sub> dramatically. C. Nicorandil eliminated EAD, shortened QT Interval and MAPD<sub>90</sub> in all sites, and decreased dispersion of MAPD<sub>90</sub>. D. Addition of propranolol completely reversed effects of epinephrine to control level. Numbers in each MAP recording show dispersion of MAPD<sub>90</sub>.
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 (Fig 3C), 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 MAPD90 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.22–25 Commensurate with this, β-blockers were reported to reduce cardiac events dramatically in LQT1 syndrome.26 Recent genetic linkage analysis studies have shown that a mutation in KvLQT1, which is responsible for LQT1 syndrome, altered the effect of the coexpression of minK and KvLQT1, which resulted in an impairment in the I_{Ks} current.27,28 β-Adrenergic stimulation increases inward current through I_{Ca,L} and outward repolarizing I_{Ks} and I_{Cf} current.29 A net increase of outward repolarizing current, because of a greater increase in I_{Ks} and I_{Cf} than in I_{Cch}, 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.29 Several experimental studies have suggested that inward current through I_{Ca,L} or through sodium-calcium exchange30 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.30

In the present study, epinephrine prolonged the MAPD_{90} and QT interval and increased the dispersion of MAPD_{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_{90} and QT interval, decreased the dispersion of MAPD_{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 vitro31,32 and in vivo34 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,35–36 clofilium,36 or Bay K 8644.37 Recently, several groups used MAP recordings and showed the effect of nicorandil in decreasing MAP duration and abolishing EADs.38–40 Our data as well as those in the previous studies suggest that I_{KATP} openers 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 KvLQT1 defect.

Propranolol in addition to nicorandil completely reversed the effect of epinephrine in prolonging the MAPD_{90} and QT interval, increasing the dispersion of MAPD_{90}, and inducing EADs as well as VPCs. The effect of β-blockers is likely to be mediated by decreasing I_{Cch} 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^+ Channel Openers**

TdP is an atypical polymorphic ventricular tachycardia most often associated with QT prolongation in both congenital and acquired forms of LQTS. Several experimental41–43 and clinical observations using MAPs12–14,16,34–36 suggested a significant role for EAD-induced triggered activity in the genesis of TdP. El-Sherif et al43 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 coworkers44,45 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 al46 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_{90}. These results suggest that the epinephrine-induced VPCs were related to the EADs. Our data also suggest that the effect of K^+ 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.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^+ 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 LQT1 syndrome, it is also important to know whether nicorandil offers any effects in addition to those of propranolol.

Acknowledgments

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References

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