Early Afterdepolarizations Induced by Isoproterenol in Patients With Congenital Long QT Syndrome

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Background. Several recent experimental and clinical studies have shown that early afterdepolarizations (EADs) are important in the genesis of QTU prolongation and ventricular tachyarrhythmias (VTs) in patients with long QT syndrome. On the other hand, sympathetic stimulation is well known to contribute to the genesis of QTU prolongation and VTs in patients with congenital long QT syndrome. The present study was performed to examine the influence of isoproterenol on the genesis of EADs and on the action potential durations and QTU intervals in patients with congenital long QT syndrome.

Methods and Results. We recorded monophasic action potentials (MAPs) with a contact electrode during right atrial pacing at a constant cycle length of 500 msec before and after continuous isoproterenol infusion (1 µg/min). MAPs were obtained from the right and left ventricular endocardium in six patients with congenital long QT syndrome (LQT group, 18 recording sites) and in eight control patients (control group, 19 recording sites). Although no EADs were recorded from either group during the control state, MAP duration at 90% repolarization (MAPD90) was significantly longer in the LQT group (n=18) than in the control group (n=19) (275±36 versus 231±22 msec; p<0.0005). Isoproterenol induced EADs in four of the six LQT patients (five of 18 recording sites) but not in the eight control patients (zero of 19 recording sites). The appearance of EADs in the LQT group was associated with an increased amplitude of the late component of the TU complex, and the corrected QT (QTc) interval was prolonged by isoproterenol from 543±53 to 600±30 msec (n=6; p<0.05). Isoproterenol also prolonged the MAPD90 from 275±36 to 304±50 msec in the LQT group (n=18; p<0.005), whereas it shortened the MAPD90 from 231±22 to 224±25 msec in the control group (n=19; p<0.05). Moreover, isoproterenol increased the dispersion of MAPD90 (difference between the longest MAPD90 and the shortest MAPD90 in each patient) from 30±5 to 62±35 msec in the LQT group (n=6; p=0.08), whereas it did not change the dispersion of MAPD90 in the control group (n=8; 25±14 versus 27±14 msec).

Conclusions. These results suggest that patients with congenital long QT syndrome have primary repolarization abnormalities and that EADs induced by isoproterenol play an important role in the exaggeration of these repolarization abnormalities. (Circulation 1991;84:1915–1923)

Several recent in vitro studies with microelectrodes and in vivo studies using monophasic action potential (MAP) recordings suggest that QTU prolongation and polymorphic ventricular tachyarrhythmias (VTs) are due to afterdepolarizations and triggered activity in acquired, and possibly also in congenital, long QT syndrome.1–4 Clinically, Gavrilicu and Luca5 recorded monophasic action potentials (MAPs) in two patients with congenital long QT syndrome and showed afterdepolarizations during the late repolarization. Bonatti et al8 also reported the appearance of humps characteristic of early afterdepolarizations (EADs) recorded on the MAPs of patients with idiopathic long QT syndrome.

On the other hand, strong emotion and physical exertion are known to precipitate syncope and sud-
den death in patients with congenital long QT syndrome. In addition, surgical interruption of the left stellate ganglion or β-adrenergic blocking drugs are reported to reduce the incidence of syncope and sudden death. These findings suggest that the sympathetic nervous system can profoundly influence the electrophysiological properties of the heart and the genesis of QTU prolongation and VTs in patients with congenital long QT syndrome. In fact, Ben-David and Zipes, using a MAP technique in an animal model of long QT syndrome produced by cesium chloride, recently suggested that ansae subclaviae stimulation or norepinephrine influences the amplitude of EADs and the prevalence of VTs.

The purpose of the present study was to examine the influence of isoproterenol (β-adrenergic receptor stimulation) on the genesis of EADs and on the action potential durations and QTU intervals in patients with congenital long QT syndrome.

Methods

Subjects

This study had a patient–control design. Inclusion criteria for patients with congenital long QT syndrome (LQT group) were 1) a corrected QT (QTc) interval of more than 0.44 sec, 2) a history of stress-induced syncpe or polymorphic VTs, and/or 3) family members with long QT syndrome. Six consecutive patients who met these criteria between November 1988 and October 1990 were entered into this study. There were five females and one male. Their ages ranged from 12 to 45 years (mean, 29 years). Four patients were familial and two patients were idiopathic. All six patients had a history of stress-induced syncpe. Polymorphic VTs characteristic of torsade de pointes were documented in four patients. The criteria for control patients (control group) included 1) a QTc interval of less than 0.44 sec and 2) no history of syncpe and VTs. There were eight control patients, consisting of six with sick sinus syndrome, one with concealed Wolff-Parkinson-White syndrome, and one with idiopathic ventricular premature contractions. There were four women and four men. Their ages ranged from 24 to 66 years (mean, 49 years).

Electrophysiological Studies

Written informed consent was obtained before the study. All the patients were studied while in a nonsedated, postabsorbed state after all antiarrhythmic medications had been discontinued for at least five drug half-lives.

Two or three standard 6F bipolar electrode catheters with 10-mm interelectrode spacing (USCI Inc.) or 6F MAP catheters (EP Technologies Inc., MAP–pacing combination catheter) were introduced through a femoral vein or an antecubital vein and advanced into the right ventricle and right atrium under fluoroscopic guidance. In all six LQT patients and in one of the eight control patients, one more standard or MAP catheter was introduced through a femoral artery into the left ventricle.

Monophasic Action Potential Recordings

MAPs were recorded simultaneously from two or three sites at the right ventricular (RV) and/or left ventricular (LV) endocardium in each patient by the contact electrode technique as described previously (LQT group, 18 sites; control group, 19 sites). MAPs along with ventricular electrograms at the same sites and six surface electrocardiographic leads and arterial pressure through a radial artery were displayed simultaneously on a strip chart recorder (Siemens-Elema, 16-channel Mingograf) at a paper speed of 100 mm/sec. Signals of MAPs were amplified and filtered at a frequency of 0.05–500 Hz, and those of the ventricular electrograms were amplified and filtered at a frequency of 50–500 Hz. Because distinction of afterdepolarizations from recording artifacts is critical on MAP recordings, MAPs were obtained after placement of the catheter electrode in a position providing continuous recordings of stable amplitude, smooth configuration, and isopotential diastolic baselines (phase 4) from a single endocardial site for at least 10 minutes during both sinus rhythm and constant atrial pacing (cycle length, 500 msec). Once the contact catheter was stabilized, MAPs could be recorded continuously from the same endocardial site for long periods without additional manipulation of the catheter.

We defined EADs as depolarizing afterpotentials that interrupted or delayed repolarization of the action potential. The duration of the MAP was determined at 90% repolarization (MAP duration at 90% repolarization, MAPD90), which included the EADs if present. The dispersion of MAPD90 was defined as the difference between the longest MAPD90 and the shortest MAPD90 in each patient. The QTU interval was determined mainly from ECG lead V1 and was defined as the time between the onset of the QRS complex and the point at which the line of maximal downslope of the T wave (or the late component of the TU complex, if present) crossed the baseline before the isoelectric UP interval. The QTU interval was corrected for heart rate (QTc) by Bazett’s method.

Protocol

Constant right atrial pacing at a basic cycle length of 500 msec was performed with 2-msec rectangular stimuli at twice diastolic threshold delivered from a programmable stimulator (Nihon Kohden Inc., SEL-3102) in both groups.

MAP recordings before isoproterenol (control state) were obtained during constant atrial pacing for at least 3 minutes until MAP duration had reached a new steady state. The MAPD90 and the QTU interval were measured from the last of a sequence of atrial paced beats. This was done to avoid interruption of the T wave and the repolarization phase of MAPs by the next pacing stimulus and the P wave.
Isoproterenol Infusion

Isoproterenol was infused at a constant rate of 1 \( \mu \text{g/min} \) in both groups. After a steady state was achieved, MAP recordings during isoproterenol infusion were obtained by the procedure described above.

Statistical Analysis

Data are given as mean±SD. Differences within groups (control state versus isoproterenol) or between groups (LQT group versus control group) were analyzed by paired and unpaired t tests. The \( \chi^2 \) test for matched pairs was used to compare the incidence of EADs. A value of \( p<0.05 \) was considered significant.

Results

Clinical Characteristics

Clinical characteristics of the six LQT patients and the eight control patients are shown in Table 1. All six LQT patients had prolonged QTc intervals (580±58 msec\(^{1/2} \) [range, 520–670 msec\(^{1/2} \)], and the interval was always abnormally prolonged in five patients. The remaining patient (patient 6) had a borderline prolonged resting QT interval at the study but had episodic QTU prolongation that was observed spontaneously in response to emotional stress or exercise. At the study, the mean QTc interval during sinus rhythm was 488±34 msec\(^{1/2} \) (range, 450–550 msec\(^{1/2} \)) in the LQT group and 389±22 msec\(^{1/2} \) (range, 360–420 msec\(^{1/2} \)) in the control group.

Data on sinus cycle length and blood pressure change with isoproterenol are shown in Table 2. Sinus cycle length shortened significantly with isoproterenol in both groups (LQT group, 752±95 to 590±50 msec, \( p<0.001 \); control group, 1,113±262 to 745±176 msec, \( p<0.001 \)). Systolic blood pressure during constant atrial pacing increased significantly with isoproterenol in both groups (LQT group, 134±10 to 150±15 mm Hg, \( p<0.05 \); control group, 137±25 to 149±21 mm Hg, \( p<0.05 \)). There was no significant difference in the change of systolic blood

<p>| Table 1. Clinical Characteristics of LQT and Control Patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Sinus rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syncope</td>
<td>Polymorphic VT</td>
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<tr>
<td>LQT group</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>F</td>
<td>Familial</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>F</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>Familial</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>Familial</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>M</td>
<td>Idiopathic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>F</td>
<td>Familial</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>VPC</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>49</td>
<td>F</td>
<td>SSS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>SSS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>F</td>
<td>SSS</td>
<td>–</td>
<td>–</td>
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<td>M</td>
<td>SSS</td>
<td>–</td>
<td>–</td>
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<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>ConWPW</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>SSS</td>
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<td>–</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>F</td>
<td>SSS</td>
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</tbody>
</table>

VT, ventricular tachyarrhythmia; SCL, sinus cycle length; QTc, corrected QT interval; VPC, ventricular premature contraction; SSS, sick sinus syndrome; ConWPW, concealed Wolff-Parkinson-White syndrome.

<p>| Table 2. Changes in Sinus Cycle Length and Blood Pressure During Atrial Pacing (500 msec) With Isoproterenol |
|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patients</th>
<th>SCL (msec)</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>LQT group</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>752±95</td>
<td>600–890</td>
<td>134±10</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>590±50*</td>
<td>500–650</td>
<td>150±15†</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1,113±262</td>
<td>760–1,460</td>
<td>137±25</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>745±176*</td>
<td>520–1,070</td>
<td>149±21†</td>
</tr>
</tbody>
</table>

Values are mean±SD.
SCL, sinus cycle length; BP, blood pressure.
*\( p<0.001 \) vs. control.
†\( p<0.05 \) vs. control.
pressure with isoproterenol between the two groups. Although diastolic blood pressure during constant atrial pacing decreased slightly with isoproterenol in both groups, this difference was not significant.

Influences of Isoproterenol on Early Afterdepolarizations

All electrophysiological data are shown in Table 3. Before isoproterenol (control state), no EADs were recorded from either group during either sinus rhythm or atrial pacing. Isoproterenol induced EADs in four of the six LQT patients (five of 18 recording sites: RV apex, one; RV septum, one; RV anterior wall, two; LV apex, one), and this was associated with an increased amplitude of the late component of the TU complex on the surface electrocardiogram (Figure 1). However, isoproterenol did not induce EADs in any of the control patients (zero of 19 recording sites) ($p<0.01$ versus LQT patients, $p<0.05$ versus LQT group recording sites) (Figure 2).

Influences of Isoproterenol on $MAPD_{90}$

During the control state, the mean $MAPD_{90}$ was significantly longer in the LQT group ($n=18$) than in the control group ($n=19$) ($275\pm36$ versus $231\pm22$ (msec).
msec; \( p < 0.0005 \). Isoproterenol prolonged the MAPD\(_{90}\) from 275±36 to 304±50 msec in the LQT group (\( p < 0.005 \)) (Figure 3A). In contrast, isoproterenol shortened the MAPD\(_{90}\) from 231±22 to 224±25 msec in the control group (\( p < 0.05 \)) (Figure 3B).

**Influences of Isoproterenol on Dispersion of MAPD\(_{90}\)**

During the control state, the mean dispersion of MAPD\(_{90}\) in the LQT group was 30±5 msec and that in the control group was 25±14 msec. There was no significant difference in the dispersion of MAPD\(_{90}\) between the two groups. However, the dispersion of MAPD\(_{90}\) increased from 30±5 to 62±35 msec with isoproterenol in the LQT group (\( p = 0.08 \)) (Figure 4A). In contrast, the dispersion of MAPD\(_{90}\) did not change with isoproterenol in the control group (25±14 versus 27±14 msec) (Figure 4B).

**Influences of Isoproterenol on QT\(_c\) Interval**

During constant atrial pacing before isoproterenol, the mean QT\(_c\) interval was significantly longer in the LQT group (\( n = 6 \)) than in the control group (\( n = 8 \)) (543±53 versus 433±18 msec\(^{1/2} \); \( p < 0.0005 \)). During constant atrial pacing after isoproterenol, the QT\(_c\) interval increased from 543±53 to 600±30 msec\(^{1/2} \) in the LQT group (\( p < 0.05 \)), and this change was associated with an increased amplitude of the late component of the TU complex (Figure 5A). The QT\(_c\) interval also increased from 433±18 to 450±9 msec\(^{1/2} \) with isoproterenol in the control group (\( p < 0.05 \), but
no TU complex abnormalities were provoked like those seen in the LQT group (Figure 5B).

**Discussion**

The major finding of this study is that isoproterenol induced EADs and prolonged MAPs associated with QTU prolongation and TU complex abnormalities in patients with congenital long QT syndrome. In addition, isoproterenol also increased the dispersion of MAP durations in patients with congenital long QT syndrome.

**Monophasic Action Potentials in Congenital Long QT Syndrome**

Several studies have pointed out a variety of morphological TU complex abnormalities on the surface electrocardiogram in patients with congenital long QT syndrome. These electrocardiographic abnormalities are characteristic and diagnostic of patients with this syndrome and are thought to reflect abnormal cardiac repolarization. Moreover, several new quantitative electrocardiographic characteristics analyzed by a computer algorithm have recently been reported to be useful in identifying patients with congenital long QT syndrome.

On the other hand, since the time course of repolarization of MAPs measured with a contact electrode has been shown to correlate closely with that of simultaneous transmembrane action potentials as recorded with a microelectrode, MAPs have been used to detect membrane phenomena and repolarization abnormalities in intact beating hearts and, most importantly, in patients with long QT syndrome. In fact, several in vivo experimental studies using MAP recordings suggested that QTU prolongation and VTs may be caused by afterdepolarizations (early or delayed) and triggered activity. Clinically, Bonatti et al found humps characteristic of EADs on MAPs recorded from the endocardium in patients with idiopathic long QT syndrome. Also, Van Hare et al recently reported a child with congenital long QT syndrome and showed abnormally long MAP durations, although EADs were not recorded.

Similarly, in the present study, the MAP durations in patients with congenital long QT syndrome were prolonged and were significantly longer than those in control patients during the control state, although EADs were not recorded. EADs were not recorded during the control state in this study, possibly because the contact catheters were not correctly positioned on the endocardial sites where EADs originated. It is also possible that sympathetic tone had not fully increased to produce EADs during the control state.

**Influences of Isoproterenol in the Genesis of Early Afterdepolarizations**

Since Yanowitz et al demonstrated that left stellate ganglion stimulation and right stellate ganglion interruption prolonged the QT interval in dogs, the hypothesis of sympathetic imbalance and dominance of left-sided sympathetic influence has been supported by several clinical and experimental observations. However, experimental models, based
on intense stimulation of the left stellate ganglion
and total interruption of the right, do not develop
QTU abnormalities and spontaneous arrhythmias as
severe as those found in the clinical syndromes. Ben-David et al\textsuperscript{10,25} recently suggested roles for an-
sae subclaviae stimulation or norepinephrine and
indicated that α- as well as β-adrenoreceptor stimu-
lation may influence cesium-induced EADs and the
prevalence of VTs in an animal model of long QT
syndrome. They hypothesized that patients with con-
genital long QT syndrome have a primary myocardial
membrane defect in repolarization, which creates
EADs and the long QTU interval, and that sympa-
thetic stimulation, primary left, could periodically
increase the amplitude of the EADs to reach thresh-
old and produce VTs. Jackman et al\textsuperscript{26,27} proposed the

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Plots of changes in dispersion of monophasic action potential duration at 90\% repolarization (dispersion of MAPD\textsubscript{90}) with isoproterenol in the LQT group (n=6) (panel A) and in the control group (n=8) (panel B). Isoproterenol increased the dispersion of MAPD\textsubscript{90} from 30±5 to 62±35 msec in the LQT group (p=0.08). In contrast, isoproterenol did not change the dispersion of MAPD\textsubscript{90} in the control group (25±14 vs. 27±14 msec).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Plots of changes in corrected QT (QT\textsubscript{c}) interval with isoproterenol in the LQT group (n=6) (panel A) and in the control group (n=8) (panel B). Isoproterenol significantly increased the QT\textsubscript{c} interval from 543±53 to 600±30 msec\textsuperscript{1/2} in the LQT group (p<0.05). Isoproterenol also increased the QT\textsubscript{c} interval from 433±18 to 450±9 msec\textsuperscript{1/2} in the control group (p<0.05).}
\end{figure}
classifications “adrenergic-dependent” and “pause-dependent” long QT syndromes to distinguish congenital from acquired long QT syndromes. They also suggested that both adrenergic-dependent and pause-dependent long QT syndromes have a similar membrane defect with diminished repolarizing currents, and that because these repolarizing currents are severely depressed in adrenergic-dependent long QT syndrome, the normal enhancement of depolarizing currents by sympathetic stimulation would lead directly to triggered firing.

In the present study, isoproterenol induced EADs in four of the six patients with congenital long QT syndrome, and this was associated with the prolongation of MAP durations and QTU intervals. The MAP durations were also prolonged by isoproterenol in the remaining two patients with congenital long QT syndrome in whom EADs were not recorded. This is in contrast to the slight shortening of MAP durations with isoproterenol in control patients. These results are compatible with the afterdepolarization hypothesis as described above, in that the patients with congenital long QT syndrome had primary repolarization abnormalities (prolonged MAP durations and QTU intervals during the control state) and isoproterenol exaggerated these repolarization abnormalities in association with the appearance of EADs.

Mechanism of Ventricular Tachyarrhythmias

The mechanism responsible for the polymorphic VTs in both congenital and acquired long QT syndrome is less clear. The arrhythmia may be due to sustained rapid EADs, oscillatory potentials triggering the first EADs, reentry resulting from the electrical heterogeneity caused by the EADs, or some other mechanism. El-Sherif et al.28,29 recently showed that the first ectopic beat arose from the peak of the EADs and the U wave, both in dogs treated with anthopleurin-A and in a case of quinidine-induced torsade de pointes. They suggested that the initiating beats of VTs are due to a triggered rhythm arising from the EADs.30 However, the mechanism of subsequent VT beats is still unclear.

Because ventricular ectopic beats and VTs were not recorded during MAP recordings either before or after isoproterenol infusion in this study, we cannot be certain of the mechanism responsible for the VTs in patients with congenital long QT syndrome. However, we speculate that the EADs induced by isoproterenol play an important role in the genesis of VTs. On the other hand, the dispersion of MAP durations also increased with isoproterenol in patients with congenital long QT syndrome, because isoproterenol induced EADs at the focal endocardium in each patient in association with prolongation of MAP durations. Therefore, we cannot exclude the possibility that the VTs are perpetuated by a reentrant mechanism caused by heterogeneous MAP durations after being initiated by EADs.31,32

Limitations

There are several limitations to this study. 1) We cannot completely exclude the possibility that some of the EADs represent recording artifacts. However, once the contact catheter was positioned at the endocardium, continuous MAP recordings with stable amplitude, smooth configuration, and isopotential diastolic baseline could be recorded throughout the study. Moreover, the appearance of EADs was always associated with morphological changes in the TU complex and QTU prolongation on the surface electrocardiogram. Therefore, we considered that the MAP recordings were stabilized, and the EADs were not artifacts in this study. 2) MAP recordings were obtained from only two or three endocardial sites in each patient. Especially in the left ventricle, MAP recordings were obtained in all patients with congenital long QT syndrome but in only one control patient. Such insufficiency and nonuniformity of the recording sites limit the calculations of dispersion of MAP durations across the entire right and left ventricles. More detailed mapping of MAP recordings is necessary to define dispersion more precisely. 3) We performed constant atrial pacing at a cycle length of 500 msec to evaluate the non-rate-dependent effects of isoproterenol on repolarization parameters. However, several studies have pointed out the direct effects of atrial pacing on QTc interval in normal subjects33–36 and in patients with congenital long QT syndrome.37 Since Bazett’s formula was drawn from data obtained from patients studied under physiological conditions at rest and after exercise, the QTc interval was reported to be prolonged slightly by an artificial increase in heart rate produced by atrial pacing.33–36 Similarly, in this study, the QTc interval was prolonged slightly by atrial pacing (without isoproterenol) from 389±22 to 433±18 msec1/2 in the control patients. Bhandari et al.37 reported a normal response of the QT interval to atrial pacing (QTc slightly increased) in patients with congenital long QT syndrome and suggested that it may have been related to the absence of any concomitant increase in adrenergic activity when the heart rate was increased. Also in this study, the QTc interval was increased by atrial pacing from 488±34 to 543±53 msec1/2 in patients with congenital long QT syndrome. Moreover, simple atrial pacing did not provoke morphological changes in the TU complex as did isoproterenol infusion. Therefore, we considered that atrial pacing was not associated with sympathetic stimulation in the present study.

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KEY WORDS • monophasic action potentials • sympathetic stimulation • ventricular tachyarrhythmias • long QTU interval
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