Sympathetic Nerve Activity in the Congenital Long-QT Syndrome

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Background—Patients with congenital long-QT syndrome (LQTS) are susceptible to life-threatening arrhythmias. The sympathetic nervous system may have an important triggering role for cardiovascular events in LQTS. We therefore examined measurements of sympathetic neural traffic in patients with LQTS and matched control subjects.

Methods and Results—Twelve patients with congenital LQTS and 12 healthy volunteers matched for age, sex, and body mass index were studied. Heart rate, respiration, blood pressure, and sympathetic nerve activity to the skeletal muscle blood vessels (muscle sympathetic nerve activity) and to the skin (skin sympathetic nerve activity) were monitored and recorded continuously. Resting heart rate (P=0.03), muscle sympathetic nerve activity burst rate (P=0.008), and burst incidence (P=0.02) were lower in patients with LQTS than in control subjects. However, skin sympathetic nerve activity was very similar in patients with LQTS and control subjects. Spectral analysis of RR variability showed a decreased low-frequency component, an increased high-frequency component, and a decrease in the ratio of the low-frequency component to the high-frequency component in patients with LQTS (P=0.01).

Conclusions—LQTS is associated with a selective reduction in sympathetic drive to muscle blood vessels and perhaps also to the heart. (Circulation. 2003;107:1844-1847.)

Key Words: nervous system, sympathetic ■ heart rate ■ long-QT syndrome ■ apnea

The congenital long-QT syndrome (LQTS) is a cardiac channelopathy characterized by prolonged ventricular repolarization and increased susceptibility to sudden cardiac death. Several cardiac ion channel genes have been established in the molecular pathogenesis of LQTS. Life-threatening arrhythmias in patients with LQTS are often related to emotional and physical stress. Before the discovery of channelopathies in the 1990s, dysfunction of the sympathetic nervous system was postulated in the pathogenesis of LQTS. Indeed, the sympathetic nervous system is a cardinal mediator of the response to stress and may have an important triggering role for cardiovascular events in LQTS.

However, characteristics of the sympathetic nervous system in patients with LQTS are unclear. We therefore compared intraneural measurements of sympathetic nerve traffic between patients with LQTS and matched control subjects. We also compared variability of RR intervals in patients with LQTS and matched control subjects to obtain insights into cardiac autonomic tone.

Methods

Twelve patients (4 men, 8 women; age 40±11 years; body mass index [BMI] 27±1 kg/m²) with congenital LQTS were studied. Mutations were documented in KVLQTI/KCNQ1 (n=5), HERG/KCNH2 (n=5), and SCN5A (n=1). One patient had a diagnosis of congenital LQTS based on family history and ECG but did not possess a mutation in any of the 5 known LQTS genes. All patients were free of any other diseases. None of the patients with LQTS were on β-blocker therapy. Three patients had implanted cardioverter-defibrillators. Twelve healthy control subjects (4 men, 8 women; age 38±9 years; BMI 26±1 kg/m²) matched for age, sex, and BMI were studied. The Mayo Foundation Institutional Review Board approved the study.

ECG was recorded continuously by ECG Bioamplifier (Gould Electronics), and respiration by a thoracic belt (Pneumotrace, Gould Electronics). Blood pressure was recorded continuously (Finapres, Ohmeda) and also measured every minute with an automatic sphygmomanometer (Dinamap, Critikon Inc.).

Multunit efferent intraneural recordings of sympathetic nerve activity to skeletal muscle blood vessels (muscle sympathetic nerve activity [MSNA]) and to skin blood vessels and sweat glands (skin sympathetic nerve activity [skin SNA]) were obtained from the peroneal nerve by using microneurography. Because of the remarkably low levels of MSNA evident in the patients with LQTS, we also obtained measures of skin SNA in 7 patients with LQTS and 7 control subjects to determine if there was a global reduction in sympathetic drive.

Study Protocol

MSNA, blood pressure, and RR interval were measured during supine rest in a quiet, undisturbed environment. Subjects were also asked to hold their breath after full expiration (end-expiratory apnea) to confirm the quality of the recording site because resting MSNA was very low in patients with LQTS.

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**Data Analysis**

The QT intervals were measured from the onset of the Q or R wave to the termination of the T wave. Corrected QT interval for heart rate (QTc) was calculated by Bazett’s formula, where \( QTc = \frac{QT}{RR^{1/2}} \). Power spectral analysis of RR interval was carried out according to established techniques. Both MSNA and skin SNA were expressed as bursts per minute. MSNA was also expressed as burst incidence (bursts per 100 heart beats).

**Statistical Analysis**

Data were expressed as mean±SEM. Differences between patients with LQTS and control subjects were analyzed by the Student unpaired t test.

**Results**

Patients with LQTS and control subjects had very similar blood pressures (Table), but resting heart rates were slower (67±3 versus 76±3 bpm, \( P=0.03 \)) in patients with LQTS. RR (\( P=0.04 \)) and QT intervals (\( P<0.0001 \)) and QTc (\( P<0.0001 \)) were greater in patients with LQTS than in control subjects. Patients with LQTS also had a decreased low-frequency (LF) variability of RR (\( P=0.007 \)) and an increased high-frequency (HF) variability (\( P=0.01 \)) compared with control subjects. The LF/HF ratio of RR variability was significantly reduced in patients with LQTS (\( P=0.006 \)).

MSNA burst rate (\( P=0.008 \)) and burst incidence (\( P=0.02 \)) were lower in patients with LQTS than in control subjects. The presence of a technically excellent recording site despite markedly reduced baseline levels of MSNA was confirmed in the patients with LQTS by testing the responses to end-expiratory apnea (Figure 1).

Skin SNA was recorded in 7 patients with LQTS and 7 control subjects matched for age, sex, and BMI. There was no difference in skin SNA between patients with LQTS and control subjects (16±2 versus 17±2 bursts/min, Figure 2).

**Comparison Between Patients With Congenital LQTS and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Patients With LQTS (n=12)</th>
<th>Control Subjects (n=12)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>85±2</td>
<td>87±3</td>
<td>NS</td>
</tr>
<tr>
<td>RR, ms</td>
<td>946±50</td>
<td>816±36</td>
<td>0.04</td>
</tr>
<tr>
<td>QT, ms</td>
<td>466±15</td>
<td>362±9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>486±7</td>
<td>399±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>316±87</td>
<td>881±169</td>
<td>0.007</td>
</tr>
<tr>
<td>LF, normalized units</td>
<td>45±26</td>
<td>69±15</td>
<td>0.01</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>944±727</td>
<td>399±145</td>
<td>0.47</td>
</tr>
<tr>
<td>HF, normalized units</td>
<td>43±7</td>
<td>22±4</td>
<td>0.01</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.5±0.4</td>
<td>3.6±0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>14±3</td>
<td>26±3</td>
<td>0.008</td>
</tr>
<tr>
<td>MSNA, bursts/100 heart beats</td>
<td>22±4</td>
<td>36±4</td>
<td>0.02</td>
</tr>
<tr>
<td>Skin SNA, bursts/min</td>
<td>16±2</td>
<td>17±2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM. NS indicates not significant.

\( ^*n=7 \) for skin SNA.

**Figure 1.** Baseline MSNA recordings over 20 seconds in patients with LQTS and control subjects, showing significantly reduced bursts rates in patients with LQTS. MSNA responses over 20 seconds at end of apnea in patients with LQTS confirm the appropriate siting of the recording electrode and show clear sympathetic responses to apnea despite low levels of tonic sympathetic activity.
Discussion

The novel findings of the present study are that patients with LQTS have very low baseline MSNA and normal skin SNA. This selective reduction of MSNA in patients with LQTS is accompanied by slower heart rates and a reduced LF power of RR variability, which is suggestive of decreased cardiac sympathetic drive. The low levels of resting MSNA and slow heart rate but normal skin sympathetic activity suggest a region-specific attenuation of sympathetic drive in these patients, rather than generalized sympathetic hypofunction.

The mechanisms linking a particular channel mutation and QT abnormalities to cardiac events are poorly understood. There is markedly variable expressivity and substantial genetic heterogeneity associated with this cardiac channelopathy. Identical mutations within the same family may be associated with very early death in one individual and with asymptomatic longevity in another. The autonomic nervous system has been cited frequently as an important trigger for cardiovascular events. However, no prior data demonstrate a clear primary autonomic abnormality in patients with LQTS. Examination of earlier studies documenting resting heart rate suggest a tendency toward slower heart rate in patients with LQTS, although this has not been previously confirmed. Our data suggest that the slower heart rate observed previously in children <3 years of age with LQTS seems to be present even in adults, when these measurements are obtained in resting undisturbed conditions and compared with closely matched control subjects. A previous study of the autonomic nervous system, in which conventional time domain, frequency domain, and nonlinear measures of heart rate variability were used, has demonstrated no difference between the patients with LQTS and control subjects, although an earlier study of heart rate variability in which Holter recordings were used suggested lower cardiac sympathetic and higher parasympathetic nervous activity.

The present study is the first objective demonstration of differences in autonomic activity as evidenced by lower sympathetic activity to muscle blood vessels and lower heart rate. Control of heart rate generally depends on complex interactions between sympathetic and vagal cardiac drive. The slower heart rate in LQTS may be explained by high vagal or low cardiac sympathetic activity, or both. Furthermore, we cannot completely exclude the possibility of an abnormality of sinus node automaticity.

Important strengths of the present study include the close matching of patients with LQTS and control subjects and the absence of β-blocker use or other disease conditions in both groups. The responses to apnea in patients with LQTS (Figure 1) confirm that the multunit intraneural recording electrodes were appropriately sited within the sympathetic nerve fascicles and yielded accurate measures of resting sympathetic drive.

Although direct evidence of decreased sympathetic traffic is clear from the intraneural recordings, any conclusions about cardiac sympathetic drive in humans can only be inferred. Support for the concept of a reduction in cardiac sympathetic drive in patients with LQTS emerges: first, from the slower heart rates; second, from the lower LF and LF/HF of RR variability; and third, from evidence that lower levels of MSNA are consistently and strongly associated with low levels of cardiac norepinephrine spillover and decreased levels of coronary sinus norepinephrine. Thus, this constellation of findings is very suggestive of a decreased level of cardiac sympathetic drive in patients with untreated LQTS.

Low cardiac and vascular sympathetic drive may lead to adrenergic receptor upregulation such that the responses to sudden surges in sympathetic drive during stressful stimuli may be potentiated. We speculate that the pathophysiology of the ion channel mutations may extend beyond abnormal cardiac repolarization per se and may include primary disturbances in neural circulatory control. Although the mechanisms and consequences of lower resting MSNA in LQTS are not yet clear, surges of sympathetic activation in response to physical or emotional stress might serve as a trigger for cardiovascular events, particularly in the setting of very low tonic levels of sympathetic drive.

Figure 2. Baseline skin SNA recordings over 30 seconds were similar in patients with LQTS and control subjects.
Acknowledgments

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