Scintigraphic Pattern of Regional Cardiac Sympathetic Innervation in Patients With Familial Long QT Syndrome Using Positron Emission Tomography

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Background. The purpose of this study was to determine whether scintigraphic evidence of cardiac sympathetic neuronal denervation is present in patients with the familial long QT syndrome. The "sympathetic imbalance" hypothesis for the familial long QT syndrome proposes that the long QT syndrome results from a congenital imbalance of sympathetic innervation of the heart caused by lower-than-normal right cardiac sympathetic activity. Although the majority of clinical features of the long QT syndrome can be understood according to this hypothesis, its validity has never been shown. Noninvasive scintigraphic evaluation of the pattern of sympathetic innervation of the heart has recently become possible with catecholamine analogues that can be taken up by sympathetic nerve terminals: radioiodinated metaiodobenzyl guanidine or C-11 hydroxyephedrine (HED).

Methods and Results. Nine affected patients, each from a separate family with familial long QT syndrome, were enrolled in this study (three men, six women; mean age, 39±16 years). Scintigraphic evaluation of the pattern of cardiac sympathetic innervation in each patient was performed with HED in conjunction with positron emission tomography. The results of scintigraphic imaging in these patients were compared with those obtained in 14 asymptomatic volunteers. Scintigraphic evaluation demonstrated that HED retention index and HED uptake normalized to blood flow were no different in patients with the familial long QT syndrome than in normal control patients.

Conclusions. Patients with the long QT syndrome have normal cardiac sympathetic innervation as assessed by HED. This finding, although not incompatible with the sympathetic imbalance hypothesis of the long QT syndrome, suggests that if a decrease in right sympathetic activity is present in patients with familial long QT syndrome, it is unlikely to be attributed to an abnormal distribution of cardiac sympathetic nerves. (Circulation 1993;87:1616–1621)

Key Words • positron emission tomography • long QT syndrome • denervation

The "sympathetic imbalance" hypothesis for the familial long QT syndrome was first proposed in 1975.1 According to this hypothesis, the long QT syndrome results from lower-than-normal right cardiac sympathetic activity. Although the majority of clinical features of the long QT syndrome can be understood according to this hypothesis, its validity has never been shown.1,2

The principle objective of this study was to assess one aspect of the "sympathetic imbalance" hypothesis for the long QT syndrome by evaluating the pattern of cardiac sympathetic innervation in patients with familial long QT syndrome. In the past, evaluation of the sympathetic nervous system of the heart was limited to invasive procedures to determine the arteriovenous differences of plasma catecholamine concentrations3 or characterization of functional changes after surgical ligation of sympathetic nerves.4 Noninvasive scintigraphic evaluation of the pattern of sympathetic innervation of the human heart has recently become possible with the development of two catecholamine analogues: radioiodinated metaiodobenzyl guanidine (MIBG) or C-11 hydroxyephedrine (HED).5–7

Methods

Patient Population

Nine affected patients, each from a separate family with the familial long QT syndrome, were enrolled in this study (Table 1). There were six women and three men with a mean age of 39±16 years. Corrected QT intervals (QTc) ranged from 490 to 620 msec (mean, 534±50 msec), and all patients had affected family
TABLE 1. Data: Patients With Familial Long QT Syndrome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>QTc (msec)</th>
<th>Most severe symptom</th>
<th>Kindred characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>F</td>
<td>520</td>
<td>Cardiac arrest</td>
<td>No. of affected generations: 4, No. of affected family members: 14, No. of symptomatic family members: 3, No. of patient's offspring affected: 0</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>F</td>
<td>500</td>
<td>Seizures</td>
<td>No. of affected generations: 3, No. of affected family members: 5, No. of symptomatic family members: 3, No. of patient's offspring affected: 1</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>F</td>
<td>500</td>
<td>Cardiac arrest</td>
<td>No. of affected generations: 3, No. of affected family members: 6, No. of symptomatic family members: 4, No. of patient's offspring affected: 0</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>M</td>
<td>570</td>
<td>Syncope</td>
<td>No. of affected generations: 4, No. of affected family members: 9, No. of symptomatic family members: 3, No. of patient's offspring affected: 4</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>F</td>
<td>620</td>
<td>Cardiac arrest</td>
<td>No. of affected generations: 3, No. of affected family members: 5, No. of symptomatic family members: 3, No. of patient's offspring affected: 3</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>M</td>
<td>490</td>
<td>Seizures</td>
<td>No. of affected generations: 2, No. of affected family members: 6, No. of symptomatic family members: 3, No. of patient's offspring affected: NA</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>F</td>
<td>490</td>
<td>Cardiac arrest</td>
<td>No. of affected generations: 2, No. of affected family members: 3, No. of symptomatic family members: 1, No. of patient's offspring affected: 2</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>F</td>
<td>520</td>
<td>Seizures</td>
<td>No. of affected generations: 2, No. of affected family members: 4, No. of symptomatic family members: 1, No. of patient's offspring affected: NA</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>M</td>
<td>600</td>
<td>None</td>
<td>No. of affected generations: 4, No. of affected family members: 30, No. of symptomatic family members: 5, No. of patient's offspring affected: 4</td>
</tr>
</tbody>
</table>

QTc, corrected QT interval. NA, not applicable (no children).
*QTc ≥450 msec with symptoms or QTc ≥470 msec without symptoms, as per Keating et al.28

Members. Eight patients had a history of syncope, seizures, or cardiac arrest, and none had congenital deafness. The one asymptomatic patient had a QTc of 600 msec and four affected children. No patient had evidence of structural heart disease on physical examination. Five patients were receiving β-blocker therapy at the time of evaluation. No patient was receiving any other medication.

The results of scintigraphic imaging in the nine patients with the long QT syndrome were compared with images obtained in a group of 14 volunteers who had no evidence of structural heart disease (eight men, six women; mean age, 38±6 years). Each participant and each volunteer signed an informed consent form approved by the Human Research Committee at the University of Michigan.

Tracer Characteristics: C-11 Hydroxyephedrine
C-11 hydroxyephedrine (HED) is a norepinephrine analogue that shares the same uptake, and vesicular storage mechanisms as naturally occurring norepinephrine. When used in conjunction with positron emission tomography (PET), HED allows noninvasive visualization of the sympathetic nervous system in the human heart. Because HED is not metabolized by monoamine oxidase in the cytosol of sympathetic nerve terminals, retained HED activity reflects the uptake and storage of HED by adrenergic nerve terminals. Animal studies have confirmed that tissue retention of HED correlates closely with the concentration of norepinephrine in tissue, and studies in transplant patients have demonstrated low nonspecific binding of HED.

Scintigraphic Imaging and Data Analysis
Scintigraphic evaluation of the pattern of sympathetic innervation and resting myocardial perfusion were performed by PET using a Siemens 931 15-slice whole-body tomograph. The pattern of sympathetic innervation was evaluated using HED, and the myocardial perfusion was evaluated using N-13 ammonia. N-13 ammonia studies were performed after the intravenous injection of 20 mCi of N-13 ammonia, which was started 4 minutes after tracer injection, and data were acquired for 10 minutes. All patients received an N-13 study. The techniques used for radiosynthesis of HED, scintigraphic imaging, and data analysis at the University of Michigan have been described previously in detail. After data acquisition, the data were corrected for attenuation and reconstructed using conventional filtered back-projection algorithm. The relative regional uptake of HED at 40 minutes (expressed as a percentage) in each of nine myocardial regions was evaluated by normalizing to maximal myocardial C-11 activity. To exclude homogeneous abnormalities of sympathetic neuronal function, the myocardial uptake of HED was also evaluated by determining the HED retention index in each of the nine regions of interest. The retention index of HED was calculated by dividing the myocardial C-11 activity at 40 minutes by the integral of the C-11 HED concentration in the arterial blood from the time of injection to 40 minutes later. Thus, both the relative and absolute myocardial uptake of HED was evaluated.

Statistical Analysis
The objective of this study was to compare the patterns of sympathetic innervation in patients with the long QT syndrome with those in a control group. To evaluate the pattern of sympathetic innervation, we determined the relative uptake and the HED retention index in every one of nine myocardial regions. A repeated-measures ANOVA was used to compare the two patient groups, based on regional differences of relative HED uptake and the retention index. The degree of regional variation was also compared in the two groups by determining the coefficient of variation (mean±SD). The regional differences within each group were also examined by the same method, using a multiple-comparison testing procedure. In these analyses, the uptake of HED was normalized to myocardial perfusion to correct for differences in the amount of myocardial tissue between myocardial regions. In all cases, a probability value of <0.05 was considered significant. All data are expressed as mean±1 SD.

Results
Figure 1 shows PET images of blood flow and HED uptake in a patient with the long QT syndrome. In this patient, as in each patient with the long QT syndrome in this study, slight inhomogeneities of blood flow and HED uptake were observed. The inhomogeneities ob-
served in patients with the long QT syndrome fell within 2 SD of normal regional HED values as assessed by the control population (Figure 2). None of the long QT patients had perfusion or HED uptake abnormalities as defined by this comparison with a control population.

The summary data of HED uptake normalized to blood flow are shown in Figure 3. In both control and long QT patients, a slight difference in normalized HED uptake was observed among the nine myocardial regions ($p<0.01$). However, the pattern of normalized HED uptake was not significantly different between the two groups.
HED UPTAKE
NORMALIZED BY BLOOD FLOW

NORMAL VOLUNTEERS

LONG QT PATIENTS

FIGURE 3. Polar map display of summary data of C-11 hydroxyephedrine (HED) uptake normalized by blood flow in 14 normal volunteers (left panel) and in nine patients with the long QT syndrome (right panel). In both control and long QT patients, a slight difference in normalized HED uptake was observed among the nine myocardial regions (p<0.01). However, the pattern of normalized HED uptake in the two groups did not differ (p=0.9). ANT, anterior; SEP, septal; LAT, lateral; INF, inferior.

uptake in the two groups was no different (p=0.9). Similarly, the corresponding coefficient of variation of normalized HED uptake for the long QT and control patients did not differ (5.7 versus 5.9, p=0.9).

Summary data of HED retention are shown in Figure 4. Differences in the HED retention index between myocardial regions were present in patients with the long QT syndrome and in normal control patients (p<0.001). However, the pattern of HED retention in the two groups was no different (p>0.2). Similarly, the coefficient of variation of the HED retention index for the long QT and control patients did not differ (0.09 versus 0.07, respectively, p=0.3). The results of HED imaging were no different in the five patients receiving β-blocker therapy versus the four untreated patients.

Discussion

The results of this study demonstrate that patients with the familial long QT syndrome have a normal scintigraphic pattern of cardiac sympathetic innervation by PET with HED. This finding suggests that the distribution and density of sympathetic nerve terminal are no different in patients with the long QT syndrome than in normal control patients.

Implications Regarding the Mechanism of the Long QT Syndrome

The sympathetic imbalance hypothesis for the familial long QT syndrome, which proposes that the long QT syndrome results from a congenital imbalance of sympathetic innervation of the heart caused by lower-than-normal right cardiac sympathetic activity, was first outlined by Schwartz et al in 1975. Although this hypothesis has never been shown conclusively, it is supported by the results of experimental studies that have demonstrated that the majority of the clinical features of the long QT syndrome can be reproduced by ablating the right stellate ganglion. Some of the key observations include: 1) ablation of the right stellate ganglion results in prolongation of the QT interval and the development of T-wave alternans, 2) ablation of the right stellate is arrhythmogenic, 3) a low resting heart rate and an impaired heart rate response to exercise are observed after right stellactomy, 4) body surface ECG potentials in patients with the long QT syndrome demonstrate prolonged repolarization in the anterior and lateral ventricular walls that are innervated primarily by right-sided sympathetic fibers, and 5) in patients with the congenital long QT syndrome, ablation of the left stellate ganglion prevents recurrence of symptoms.

If the sympathetic imbalance hypothesis for the long QT syndrome is correct, the congenitally decreased right sympathetic activity could reflect abnormalities at any level of the sympathetic axis, including the brain, sympathetic chain, adrenergic nerve terminals, β-receptor density and/or function, or at the postreceptor level. The purpose of this study was to evaluate one element of the sympathetic axis, namely, the adrenergic nerve terminals. The present demonstration of a normal pattern of HED uptake and retention provides strong evidence that the density and distribution of cardiac sympathetic nerve terminals in patients with the familial
long QT syndrome are no different from that in the normal population. This finding, although not incompatible with the sympathetic imbalance hypothesis of the long QT syndrome, suggests that if a decrease in right sympathetic activity is present in patients with the familial long QT syndrome, it is unlikely to be attributed to an abnormal distribution of cardiac sympathetic neurons. It remains possible, however, that differences in regional sympathetic tone may be present in patients with the long QT syndrome despite a normal density and distribution of sympathetic nerve terminals caused by differences in sympathetic nerve terminal discharge. On the other hand, our finding is consistent with the "primary myocardial abnormality" hypothesis, which proposes that the long QT syndrome results from an inherited defect in one or more myocardial ion channel proteins involved in repolarization.20–22

**Comparison With Prior Studies**

This is the first study to evaluate the pattern of cardiac sympathetic innervation in patients with the long QT syndrome using HED in conjunction with PET. However, the results of this study are in contrast to those of Gohl et al,23 who recently reported the presence of an inhomogeneous scintigraphic pattern of sympathetic innervation in patients with the long QT syndrome. In the latter study, decreased uptake of the radiotracer (MIBG) was detected in the inferior and inferoseptal wall of the left ventricle.23

There are several important methodological differences in these two studies that may explain, at least in part, their disparate findings. First, in the present study, HED in conjunction with PET was used to image sympathetic innervation, whereas Gohl et al23 used MIBG in conjunction with conventional scintigraphic imaging. Like HED, MIBG is a norepinephrine analogue that when labeled with I-123 can be detected scintigraphically and, therefore, can be used to noninvasively image the cardiac sympathetic nervous system.5,6,24 However, MIBG is more lipophilic than HED, resulting in greater nonspecific binding of the former to myocyte membranes. Other important advantages of HED imaging in conjunction with PET are that it allows for a quantitative analysis of the pattern of sympathetic innervation and is not susceptible to attenuation by overlying tissues because it is attenuation corrected. In contrast to single-photon emission tomography, the HED images were obtained with PET. This technique allows for attenuation correction that provides a superior image quality. Such attenuation correction is performed using a transmission scan acquired before the injection of the radiotracer. This transmission scan allows the generation of an attenuation map, which is then used to correct subsequent emission data. A second difference in the two studies is that different patient populations were evaluated. In the present study, eight of nine patients were symptomatic, all had a prolonged QT interval, and all patients, each from a distinct family, had at least two affected blood relatives. In contrast, in the study by Gohl et al,23 only four of the 12 patients studied had both symptoms and QT prolongation. Furthermore, only two of these four patients, both from the same family, had clear evidence of family involvement. Seven of the remaining eight patients were asymptomatic. Although the results of the present study are in contrast to those of Gohl et al,23...
they are consistent with unpublished data from Zipes and Miyazaki,26 who recently described two patients with the long QT syndrome, both of whom had a normal pattern of sympathetic innervation as assessed by MIBG scans.

Limitations

Five patients with the long QT syndrome who participated in this study were receiving β-blocker therapy at the time of scintigraphic imaging. It is unlikely that the findings of this study can be attributed to β-blocker therapy for the following reasons: 1) β-blockers do not affect the presynaptic uptake of norepinephrine, 2) the results of HED imaging were no different in the five patients receiving β-blocker therapy versus the four untreated patients, and 3) a recent study in animal hearts performed before and during β-blocker therapy showed no affect on the pattern of HED uptake (unpublished observation). It should also be mentioned that familial long QT syndrome may exhibit genetic heterogeneity26,27 and may not be limited to an abnormality reported to be tightly linked to a DNA marker on the short arm of chromosome 11.28 Hence, our negative results, although consistent in all nine patients studied, may not apply to all genetic variants of the familial long QT syndrome.

Conclusions

The results of this study demonstrate that cardiac sympathetic innervation in patients with the long QT syndrome as assessed by PET is normal. Thus, the sympathetic innervation hypothesis for the familial long QT syndrome remains to be shown conclusively. Further studies will be required to determine the precise mechanism of the long QT syndrome.

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