Cardiac retention of [$^{11}$C]HED in genotyped long QT patients:
a potential amplifier role for severity of the disease

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CONGENITAL LONG QT SYNDROME (LQTS) is associated with several gene mutations, all of which encode cardiac ion channels involved in the control of ventricular repolarization. Five culprit genes on chromosomes 3, 7, 11, and 21 were identified in Romano-Ward syndrome (31). All code for subunits of K$^+$ or Na$^+$ channels: two α-subunits of K$^+$ channels (KCNY1 for LQT1 and HERG for LQT2), the α-subunit of the Na$^+$ channel associated with Na$^+$ channel current (I$_{Na}$) (SCN5A for LQT3), and two regulatory subunits of K$^+$ channels minK (KCNE1 for LQT5 regulating KCNQ1) and MiRP1 (KCNE2 for LQT6 regulating HERG) (31). These major genetic findings have temporarily pushed into the background the three pivotal roles attributed to the sympathetic nervous system in LQTS: a pathogenic role, a triggering role, and a role as the therapeutic target, but a new modifier role has been proposed (22). Unbalanced sympathetic innervation was suggested to be the substrate (pathogenic role) (21, 25) and a sudden increase in sympathetic tone to be the trigger for the occurrence of life-threatening arrhythmia (triggering role) (17, 21, 36). On the basis of this working hypothesis, therapy with β-blockers and left sympathetic denervation are highly successful in preventing sudden cardiac death (role as therapeutic target) (17, 23). Because the severity of the disease could greatly differ among LQTS patients carrying identical gene defects, differential sympathetic activity [i.e., differences in the amount of norepinephrine (NE) or in adrenergic receptor distribution] has been suggested as playing a role leading to modifying the propensity toward life-threatening arrhythmia (modifier role) (22).

Given that regional heterogeneity in cardiac sympathetic activity could play a modifier role of arrhythmogenicity in LQTS, several attempts have been performed to noninvasively investigate presynaptic cardiac symp-

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pathetic nerve activity by single-photon emission tomography (SPECT) or positron emission tomography (PET). However, $[^{123}]$iodobenzylguanidine ($[^{123}]$MBG) SPECT studies (11, 19, 34) and $[^{11}C]$hydroxyephedrine ($[^{11}C]$HED) PET studies (5) have given contradictory results. None of these studies were performed in genotyped LQTS patients.

Because recent data have emphasized the relationship between phenotype (i.e., symptoms) and genotype in LQTS, the purpose of this study was to evaluate cardiac sympathetic innervation with $[^{11}C]$HED PET in genotyped LQTS patients.

**METHODS**

**Populations**

Eleven patients and eight controls were studied with their written informed consent according to the Declaration of Helsinki. LQTS was defined according to established diagnostic criteria (24). Patients belonged to five different families with Romano-Ward syndrome (population characteristics are shown in Table 1). LQTS patients having a clinical history of diabetes, hypertension, or hypercholesterolemia were not included in the study, nor were LQTS patients with any other cardiac disease. At the time of diagnosis, patients with syncope, recuperated cardiorespiratory arrest, and torsades de pointes were considered symptomatic. All patients were asymptomatic at the time of the study. Eight of eleven patients were receiving β-blockers at the time of evaluation (Table 1). No patient was receiving any other medication. The QT interval measurements were done in leads II and V5, and values were corrected for heart rate (QTc, Bazett’s formula). The QTc interval in patients (Table 1) was unrelated to electrolyte abnormality or any other cause of QT prolongation.

Five of eight controls belonged to four of the five studied families. The absence of cardiac disease was established through detailed history, physical examination, and 12-lead resting ECG. All controls had normal QTc intervals.

**Genetic Analysis**

Patients (Table 1) and controls were genotyped. Genomic DNA was prepared from peripheral blood lymphocytes by standard methods. PCR amplifications of exonic and juxtaexonic sequences of KCNQ1, HERG, KCNE1, KCNE2, and SCN5A genes were produced using previously published primer sequences (1, 4, 6, 30, 32). Screening of mutations was performed either by single-strand conformational polymorphism analysis (Lyon, France) or denaturing high-performance liquid chromatography (DHPLC) (Paris, France), followed by the sequencing of the abnormal PCR fragments on a ABI377 sequencer. In the Nantes laboratory, mutation analysis was conducted by direct sequencing of the genes on a ABI377 sequencer. One hundred chromosomes from unrelated control subjects were screened for unknown mutations.

**PET Acquisitions and Analysis**

One hour before data acquisition, patients and controls stayed in the supine position in a quiet ambiance. PET studies were performed on a Siemens/ECAT EXACT HR+ 63-slice whole body tomograph.

**Perfusion assessment.** $\text{H}_2^{15}\text{O}$ (185 MBq) was injected intravenously over 10 s. Data acquisition lasted 5 min, and emission scans were reconstructed in a 128 × 128 matrix using a Hanning filter with a cutoff frequency of 0.15 mm$^{-1}$. The scan sequence consisted of 22 frames: 10 images × 4 s, 2 images × 10 s, 6 images × 20 s, and 4 images × 30 s.

**Neural NE retention assessment.** NE retention was measured 20 min after $\text{H}_2^{15}\text{O}$ PET scans by using the catecholamine analog $[^{11}C]$HED. $[^{11}C]$HED PET scans were acquired after the injection of 167 MBq/kg $[^{11}C]$HED. Data acquisition lasted 40 min, and emission scans were reconstructed in a 128 × 128 matrix using a Hanning filter with a cutoff frequency of 0.15 mm$^{-1}$. The scan sequence consisted of 14 frames: 6 images × 30 s, 2 images × 60 s, 2 images × 150 s, 2 images × 300 s, and 2 images × 600 s.

**Image processing and analysis.** A $\text{H}_2^{15}\text{O}$ dynamic series was used to obtain myocardial factor images using a factor analysis of medical image sequences (FAMIS) (2, 7, 13). This method estimates a reduced number of factor curves (contained in the signal intensity curves associated with each

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**Table 1. Patients characteristics**

<table>
<thead>
<tr>
<th>Family</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Ion Channel Gene (type)</th>
<th>Mutation</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>QTc, ms</th>
<th>HR, beats/min</th>
<th>SP/DP, mmHg</th>
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<tr>
<td><strong>Family I</strong></td>
<td></td>
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<tr>
<td>Patient 1</td>
<td>47</td>
<td>M</td>
<td>HERG (LQT2)</td>
<td>A561T</td>
<td>None</td>
<td>Sel-ββ</td>
<td>460</td>
<td>42</td>
<td>104/64</td>
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<td>43</td>
<td>F</td>
<td>HERG (LQT2)</td>
<td>A561T</td>
<td>XS; RCRA; TDP</td>
<td>None</td>
<td>580</td>
<td>47</td>
<td>107/68</td>
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<td>F</td>
<td>HERG (LQT2)</td>
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<td>Non-Sel-ββ</td>
<td>540</td>
<td>58</td>
<td>114/62</td>
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<td>?</td>
<td>RCRA</td>
<td>Sel-ββ</td>
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<td>59</td>
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<td>?</td>
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<td>Sel-ββ</td>
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<td>51</td>
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<td>KCNQ1 (LQT1)</td>
<td>A371T</td>
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<td>Sel-ββ</td>
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<td>97/56</td>
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<td>M</td>
<td>KCNQ1 (LQT1)</td>
<td>F296L</td>
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<td>440</td>
<td>60</td>
<td>126/72</td>
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<td>?</td>
<td>XS</td>
<td>Sel-ββ+PM</td>
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<td>None</td>
<td>440</td>
<td>79</td>
<td>129/70</td>
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</tbody>
</table>

M, male; F, female. Symptoms at the time of diagnosis: XS, multiple syncopes; RCRA, recuperated cardiorespiratory arrest; TDP, torsades de pointes. ?, Unknown; Sel-ββ, selective β-blockers; PM, pacemaker; QTc, corrected QT interval; HR, SP, and DP, heart rate and systolic and diastolic pressure at the time of the positron emission tomography (PET) study.
excluded from analysis because of the partial volume effect. Thus 36 sectors (each sector = 5–10 g tissue) were analyzed.

Myocardial factor images (Fig. 2) were used to construct polar maps representing relative perfusion ($H_2O_9\%$) (2, 13). Mean sectorial $H_2O_9\%$ was computed as a percentage of the maximal intensity.

$[^{11}C]HED$ absolute retention ($HED_{rel}$; the averaged activity from 20 to 40 min/the integral of the $[^{11}C]$ activity input function; $\%$/min) and relative $[^{11}C]HED$ retention ($HED_{rel}$; percentage of the maximal retention) were depicted as polar maps (Fig. 1). Mean values of $HED_{rel}$ and $HED_{rel}$ for controls (control databases) and patients were available for each sector. Polar maps of each patient were compared with control databases, and sectors with a value 2SD below the mean for controls were defined as “outside sectors.”

Relative $[^{11}C]HED$ retention normalized to perfusion was computed by dividing sectorial values of $HED_{rel}$ by values of $H_2O_9\%$. Outside sectors of $HED_{rel}/H_2O_9\%$ were defined following the same criterion explained above.

**Statistical Analysis**

Values are presented as means ± SD. Normal distribution of data and SD were tested with Kolmogorov-Smirnov and equal variance tests, respectively. Global and sectorial differences between groups were tested by use of ANOVA. When no equal variance between groups was found, the nonparametric Kolmogorov-Smirnov test was used. Frequencies and proportions of outside sectors in both groups were analyzed using the $\chi^2$ test for contingency tables. $P < 0.05$ was defined as statistically significant.

**RESULTS**

**Genotypic and Phenotypic Characteristics**

Ion channel gene types, mutations, and phenotype expressions are detailed in Table 1. Mutations were identified in three of the five LQTS families. In family I, the A561T HERG mutation (6, 18) was identified, which affects the S5 domain of the channel. Families III and IV presented distinct mutations in the KCNQ1 gene resulting in amino acid change in domains framing the pore. The A371T missense mutation (family III) previously published by Donger et al. (8) was located in the S6 COOH-terminal region. A novel F296L mutation was identified in family IV, occurring in the S5...
domain of the protein. This mutation was not found in the study of the 100 unrelated control subjects.

No mutations could be identified in families II and V. The ECG profile of family II was characteristic of HERG alteration, but screening of the HERG gene by DHPLC did not display any abnormal profile. Analysis of the other genes by DHPLC (KCQ1) or SSCP (KCNE1, KCNE2, and SCN5A) gave normal results. Haplotype analyses were performed on family V using microsatellite markers for all six LQT loci. Only LQT2 markers revealed a potential cosegregation of a disease haplotype in affected patients, suggesting that a mutation in HERG could still cause LQTS in this family. A R1047L mutation was found in patient 9 (family V), but it did not cosegregate with the disease. Furthermore, the R1047L mutation was previously reported as a polymorphism in the Finnish population (14). The sequences of exonic regions of SCN5A, KCQ1, KCNE1, and KCNE2 genes were also normal for patients 9–11 (family V). The failure to identify HERG mutations in families II and V may thus result from incomplete sensitivities of analytic methods or the presence of mutations in promoter or regulatory sequences.

No LQTS-related mutations were identified in controls.

**H215O Analysis**

Two short-axis factor images of myocardial perfusion from a control and patient are shown in Fig. 2. Polar maps of perfusion were computed from these factor images.

No sectorial differences between groups were found (Table 2). Variability of perfusion among all sectors (288 in controls and 396 in patients) was similar in

| Anterior A1 62 ± 8 68 ± 7 78 ± 5 77 ± 6 1 1.34 ± 0.10 1.12 ± 0.20* 7 A2 63 ± 9 69 ± 10 79 ± 7 72.5 ± 5* 1 1.31 ± 0.13 1.08 ± 0.18* 5 A3 72 ± 15 76 ± 11 81 ± 11 74 ± 5 0 1.17 ± 0.16 1.00 ± 0.20 3 A4 63 ± 7 72 ± 8 83 ± 4 82 ± 5 0 1.37 ± 0.11 1.12 ± 0.13* 9 A5 68 ± 12 76 ± 9 87 ± 5 83 ± 8 1 1.33 ± 0.2 1.10 ± 0.15* 2 A6 75 ± 10 83 ± 10 91 ± 6 83.7 ± 3 3 1.26 ± 0.23 1.02 ± 0.15 2 A7 74 ± 15 75 ± 8 83 ± 4 82.5 ± 1 1 1.17 ± 0.21 1.10 ± 0.14 0 A8 74 ± 8 80 ± 8 83 ± 5 81 ± 7 1 1.17 ± 0.12 1.01 ± 0.12* 2 A9 76 ± 10 83 ± 8 83 ± 8 78 ± 9 1 1.12 ± 0.16 0.95 ± 0.16* 2 Lateral L1 72 ± 12 78 ± 10 79 ± 11 71 ± 6 0 1.13 ± 0.17 0.93 ± 0.16* 2 L2 75 ± 10 76 ± 11 78 ± 6 71.7 ± 5* 2 1.06 ± 0.19 0.95 ± 0.15 1 L3 78 ± 7 74 ± 10 79 ± 6 75 ± 8 3 1.02 ± 0.18 1.03 ± 0.14 0 L4 74 ± 14 80 ± 11 82 ± 7 77 ± 7 1 1.15 ± 0.17 0.98 ± 0.18 2 L5 81 ± 9 80 ± 8 82 ± 5 80 ± 7 3 1.04 ± 0.16 1.01 ± 0.12 0 L6 89 ± 6 81 ± 13 90 ± 6 88 ± 6 0 0.98 ± 0.12 1.12 ± 0.26 0 L7 73 ± 11 79 ± 9 80 ± 7 75 ± 8 1 1.13 ± 0.2 0.96 ± 0.14 1 L8 77 ± 4 79 ± 12 81 ± 4 79 ± 7 4 1.06 ± 0.08 1.02 ± 0.15 3 L9 78 ± 12 79 ± 15 82 ± 6 82 ± 9 1 1.13 ± 0.16 1.08 ± 0.22 0 Inferior I1 73 ± 10 69 ± 13 77 ± 6 76 ± 11 3 1.01 ± 0.22 1.15 ± 0.23 0 I2 73 ± 11 68 ± 13 80 ± 6 75 ± 9 2 1.10 ± 0.22 1.19 ± 0.25 0 I3 75 ± 11 69 ± 11 79 ± 6 77 ± 4 0 1.10 ± 0.25 1.16 ± 0.2 0 I4 90 ± 14 83 ± 15 88 ± 8 90 ± 7 0 0.99 ± 0.15 1.12 ± 0.26 0 I5 84 ± 11 78 ± 13 85 ± 6 90 ± 6 0 1.02 ± 0.13 1.17 ± 0.19 0 I6 80 ± 7 77 ± 11 89 ± 6 91 ± 3 0 1.13 ± 0.13 1.23 ± 0.2 0 I7 78 ± 17 74 ± 15 77 ± 8 77 ± 10 0 1.06 ± 0.21 1.08 ± 0.22 0 I8 74 ± 13 73 ± 9 75 ± 9 76 ± 9 4 1.04 ± 0.24 1.16 ± 0.26 0 I9 72 ± 10 69 ± 12 81 ± 8 82 ± 7 0 1.12 ± 0.12 1.23 ± 0.27 0 Septal S1 75 ± 7 67 ± 11 80 ± 10 78 ± 7 0 1.07 ± 0.11 1.21 ± 0.2 0 S2 76 ± 9 73 ± 9 83 ± 10 82 ± 7 0 1.11 ± 0.2 1.16 ± 0.13 0 S3 68 ± 6 74 ± 8 85 ± 6 85 ± 6 1 1.31 ± 0.12 1.16 ± 0.09* 2 S4 80 ± 11 78 ± 10 92 ± 5 92 ± 5 1 1.18 ± 0.2 1.20 ± 0.18 0 S5 76 ± 13 80 ± 7 93 ± 5 82 ± 7 0 1.26 ± 0.22 1.16 ± 0.09 0 S6 72 ± 12 77 ± 8 90 ± 4 90 ± 6 2 1.31 ± 0.27 1.16 ± 0.11 0 S7 72 ± 8 72 ± 9 88 ± 6 86 ± 5 1 1.21 ± 0.19 1.22 ± 0.20 0 S8 73 ± 13 77 ± 9 90 ± 5 86 ± 4 1 1.26 ± 0.27 1.14 ± 0.2 0 S9 78 ± 16 76 ± 10 87 ± 4 83 ± 4 1 1.16 ± 0.29 1.11 ± 0.18 0

Values are means ± SD. Sectorial mean values were grouped in anterior (A), lateral (L), inferior (I), and septal (S) territories (see Fig. 1). H215O, relative perfusion; HED95, relative [11C]hydroxyephedrine ([11C]HED) retention; Number out, number of “outside” sectors in patients (value 2SD below the mean of controls). *P < 0.05 vs. control.

Table 2. Perfusion, [11C]HED retention, and [11C]HED normalized to perfusion in controls and patients

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both groups (variances 140.4 and 126.6, \(P = 0.35\)), and global perfusion (i.e., mean perfusion in the whole left ventricle) did not differ between groups (74.8% and 75.9% for controls and patients, \(P = 0.2\)).

**HED Analysis**

The mean of HED\(_{\text{Ret}}\) for all sectors showed a small decrease in patients (12.2 ± 2.8 vs. 14.1 ± 3.3%/min in controls, \(P < 0.01\)), without significant differences when looking at the highest values: 15.3 ± 3.2%/min in patients (\(n = 11\)) and 17.1 ± 3.7%/min in controls (\(n = 8\)) (\(P = 0.25\)).

Similar to HED\(_{\text{Ret}}\), global HED\(_{\text{%Ret}}\) was lower in patients related to controls: 81.0 ± 8.8% vs. 83.3 ± 7.9% (\(P < 0.01\)).

In patients, three sectors showed a decreased average HED\(_{\text{%Ret}}\) related to controls (Table 2 and Fig. 3).

Furthermore, the number of outside sectors when looking at HED\(_{\text{%Ret}}\) was significantly higher in patients (36 sectors distributed in 9 patients) than in controls (3 sectors belonging to 3 controls; \(\chi^2 = 16.8\) for number of sectors “up” or “down” in each group, \(P < 0.01\); Table 2 and Fig. 3).

**HED\(_{\text{%Ret}}\) Normalized to Perfusion**

The average ratio of HED\(_{\text{%Ret}}\) to \(H_2O\%\) for all sectors was lower in patients (1.102 ± 0.196 vs. 1.151 ± 0.205 in controls, \(P < 0.01\)).

The patients showed a reduced averaged ratio of HED\(_{\text{%Ret}}\) to \(H_2O\%\) in nine sectors compared with controls (Table 2 and Fig. 4). These sectors were localized in the anteroseptal and anterolateral walls (Fig. 4).

When compared with the normal database, 2 outside sectors from 2 controls and 43 outside sectors from 10 patients were found (\(\chi^2 = 23.5\), \(P < 0.01\); Table 2 and Fig. 4). In patients, outside sectors were localized in the septal, anterior, and lateral walls (Fig. 4).

The distribution of outside sectors in symptomatic or asymptomatic patients is shown in Fig. 5. The five
symptomatic patients were more likely to have outside sectors (33 of 180 sectors in symptomatic patients vs. 10 of 216 sectors in asymptomatic patients, χ² = 14.0, P < 0.01).

Discussion

This study showed that most genotyped LQTS patients have a heterogeneous and decreased cardiac retention of [11C]HED in the septal, anterior, and lateral left ventricular walls. Moreover, all symptomatic patients with prior life-threatening arrhythmia showed a large number of sectors (≥3) with decreased [11C]HED retention, suggesting a possible relationship between the extension of [11C]HED impairment and the clinical severity of the disease.

Implications Regarding the Pathogenic Role of Cardiac Sympathetic Nerve Terminals in LQTS

As for [123I]MIBG, decreased retention of [11C]HED could be observed when there were abnormalities in myocardial sympathetic nerve terminals (decreased nerve fiber density, impaired uptake-1 function) or increased neuronal firing reflecting augmented sympathetic activity (because increasing NE release leads to competitive inhibition of [11C]HED reuptake). All possibilities implicate disparate levels of NE reaching myocardial cells. Yamanari et al. (34) reported insufficiencies implicate disparate levels of NE reaching myocardial cells. This is the major finding of our study. As suggested by Schwartz et al. (22), this heterogeneity could play a modifier role as a substrate of reentry for life-threatening ventricular arrhythmias.

It is well known that some forms of congenital and acquired LQTS are exquisitely sensitive to adrenergic stimulation (16, 25, 27, 36). Schwartz et al. (26) reported that life-threatening arrhythmia in 670 LQTS patients tended to occur under specific circumstances in a gene-specific manner. LQT1 patients [i.e., those with mutations affecting slow component of the delayed rectifier K⁺ current (Iₖs)] experienced the majority of their lethal cardiac events during sympathetic activation characterized by exercise or emotional stress (88%). In contrast, sympathetic activation occurs in only 56% of LQT2 [i.e., those with mutations affecting the rapid component of the delay rectifier K⁺ current (Iₛ)] and 33% of LQT3 [i.e., those with mutations affecting Iₖs]. Furthermore, a sudden auditory stimulus is the predominant trigger in LQT2 (33).

There is experimental evidence of the differential effect of β-adrenergic agonists and antagonists in LQT1, LQT2, and LQT3 models of the LQTS (27). Under normal conditions, the abbreviation of action potential duration (APD) and of QT interval duration in response to β-adrenergic stimulation is due to a relatively large increase of Iₖs and Ca²⁺-activated Cl⁻ current [IₖCaCl] versus Na⁺/Ca²⁺ exchange current (IₙaCa). In LQT1 patients, a defect in Iₖs, especially in M cells, could account for the failure of β-adrenergic stimulation to abbreviate the APD and QT interval (3, 20, 28). Among the three transmural cell types, M cells have an intrinsically smaller Iₖs (15). The disparate effects of β-adrenergic stimulation on the three cell types results in a persistent increase of transmural dispersion of repolarization and in the development of spontaneous as well as induced life-threatening arrhythmia (27). In the LQT2 model, isoproterenol transiently prolongs the APD of the M cell, possibly due to a more rapid increase of IₙaCa than of Iₖs. As a consequence, transmural dispersion of repolarization and the incidence of life-threatening arrhythmia are only transiently increased (27).

The above experimental and clinical observations indicate that the “arrhythmogenic substrate” given by genetic mutations in LQTS could be greatly influenced by sympathetic activity and that transmural dispersion of repolarization (i.e., the substrate of reentry) is modified by adrenergic stimulation. In our study, the greater quantity of outside sectors found in symptomatic patients at the time of diagnosis suggests that heterogeneous sympathetic activity could act by amplifying existing differences in transmural dispersion of repolarization in LQTS. In this way, heterogeneous sympathetic activity could be considered as having an amplifier role able to raise the propensity toward life-threatening arrhythmia and could partially explain the distinct severity of the disease within a family.
Comparison With Prior Studies

There have been several studies on cardiac sympathetic innervation assessed by [123I]MBG SPECT (11, 19, 34) and only one using [11C]HED PET (5) in LQTS patients. However, none of these studies was performed in genotyped patients. The results using [123I]MBG SPECT (11, 19, 34) showed decreased regional retention in patients. Moreover, the heterogeneity was found in the septal and anterolateral walls. In contrast, the PET study (5) showed no differences in [11C]HED retention between LQTS and controls. These discrepancies with our study could be partially explained by differences in the patient population and employed methods (number of sectors for analysis and perfusion tracers). First, these authors reported negative results in nongenotyped patients. The population of patients in our study is likely K+ channel related, and no patients with Na+ channel mutations were found. Moreover, Calkins et al. (5) drew 9 sectors for analysis on the polar map, whereas 36 sectors were taken into account in our study. The tomograph used in the present study reaches better resolution and sensitivity than the Siemens 931 15-slice tomograph employed by these authors, and it allowed us to increase the number of sectors for analysis. Designed sectors on the polar map represent 10-fold volumes that could be discriminated by the camera. Finally, differences from the use of [13N]ammonia or H215O/FAMIS to evaluate perfusion could be addressed. In the dysfunctional ischemic myocardium, H215O yields higher absolute myocardial blood flow values those of [13N]ammonia (10). Nevertheless, so far no studies support the idea of perfusion abnormalities in LQTS, which is confirmed by our results and by the clinical history of patients. Thus ischemic territories in LQTS patients are unlikely, and confounding factors from referred discordance are negligible.

Limitations of the Study

The main limitation of this study as well as that of all previous scintigraphic studies (5, 11, 19, 34) is the small number of investigated patients. Comparison to normal database for outside sector detection—a way to partially circumvent this limitation—showed clear differences between controls and patients, which were concordant with sectorial mean differences between both groups. Nevertheless, the small number of patients probably prevents a better separation between patients with and without symptoms. Therefore, we concluded about the existence of heterogeneity in [11C]HED retention in patients, and we suggest that the degree of this heterogeneity is related to the severity of the disease.

During the PET study, 8 of 11 patients and none of the controls were on β-blockers, and so the two populations differed on an important point. Indeed, cardiac [11C]HED retention could hypothetically be modified by β-blockers. [11C]HED basically traces the presynaptic reuptake of catecholamines (uptake 1). This mechanism accounts for 70% of NE released from the nerve terminal. Few studies have focused on the effects of β-blockers on uptake 1. Ziegler et al. (35) studied the plasmatic clearance of NE and infused isoproterenol in controls and Shy-Drager patients. By analyzing the effect of propranolol on NE clearance, they suggested that propranolol acts on extraneural accumulation (uptake 2) rather than on uptake 1. Nevertheless, one must be cautious when getting conclusions regarding the plasmatic behavior of NE and isoproterenol, which could not reflect cardiac uptake 1. Looking at the extraneural accumulation (uptake 2) and metabolism of NE, it has been proved in isolated rat hearts that it can be partially inhibited by the addition of β-blockers (9). Because a small amount of NE enter the cardiac cell by uptake 2, this effect is likely negligible. Finally, blockade of prejunctional β-adrenoceptors, whose stimulation induces NE release (12), could modify the amount of retained [11C]HED. This effect should be restricted to patients taking nonselective β-antagonists, because human prejunctional β-adrenoceptors are predominantly of the β2 subtype (12). In our population, six of eight patients were receiving selective β-blockers. The three untreated patients presented a small number of outside sectors when [11C]HED retention was normal-zed to perfusion. Unfortunately, the number of patients off therapy is too small to allow inferences on β-blocker effects. Similarly, in a small population, Calkins et al. (5) noticed that the results of [11C]HED imaging were not different in the five LQTS patients receiving β-blockers versus the four untreated patients. In summary, even if the question remains unanswered, all available information allowed us to suppose a moderate impact of β-blockers on [11C]HED retention.

In conclusion, genotyped LQTS patients have a heterogeneous and decreased cardiac retention of [11C]HED in the septal, anterior, and lateral left ventricular walls. The larger number of heterogeneous sectors in symptomatic patients suggests that sympathetic function could play an amplifier role in the severity of the disease.

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DISCLOSURES

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