QT-interval variability and autonomic control in hypertensive subjects with left ventricular hypertrophy

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ABSTRACT

Left ventricular hypertrophy is a risk factor for sudden death. Malignant ventricular arrhythmias originate from altered cardiac repolarization. Ample data have described spatial abnormalities in cardiac repolarization [QT interval (QT) dispersion] in subjects with hypertension; more data are needed on temporal changes. This study was designed to assess the QT variability index (QTVI), the slope between QT and the RR interval (QT–RRslope) and spectral QT variability in subjects with arterial hypertension. The results were compared with those from a population at high risk of sudden death, i.e. patients with hypertrophic cardiomyopathy (HCM) who had received an implantable cardioverter/defibrillator (ICD), and those from normotensive control subjects. A total of 44 hypertensive subjects, six patients with HCM and an ICD and 33 control subjects underwent simultaneous short-term recording (256 beats) of QT, RR and systolic blood pressure variability, in the supine position, during controlled breathing. QTVI and spectral components of QT variability in the hypertensive group were significantly higher than in normotensive control subjects (P < 0.001), but significantly lower than in patients with HCM and an ICD (P < 0.001). The severity of left ventricular hypertrophy correlated significantly with QTVI and the ratio of low-frequency (LF) to high-frequency (HF) power obtained from the RR variability spectra (RRLF/HF, slope = 0.24, P < 0.05; QTVI, slope = 4.06, P < 0.0001; intercept, slope = 2.40, P < 0.05; RRLF/HF, P < 0.0001). The QT–RR slope was significantly higher only in patients with HCM and an ICD (P < 0.001). In conclusion, the increased QTVI and the correlation of this index with left ventricular hypertrophy indicates that hypertension increases temporal cardiac repolarization abnormalities. At the level of the cardiac sinus node, this alteration is associated with increased sympathetic and reduced vagal modulation. As already noted in patients with HCM, the increased QTVI could be a factor responsible for triggering malignant ventricular arrhythmias in subjects with hypertension.

Key words: autonomic nervous system, hypertension, QT, QT dynamic, spectrum analysis, sudden death, ventricular hypertrophy.

Abbreviations: HCM, hypertrophic cardiomyopathy; HF, high-frequency; ICD, implantable cardioverter/defibrillator; LF, low-frequency; LVMI, left ventricular mass index; n.u., normalized units; QT, QT interval; QTc, QT interval corrected for heart rate; QTVI, QT interval variability index; QTm, mean of 256 QT intervals; QTv, variance of 256 QT intervals; QT–RRslope slope between QT interval and RR interval; RR, RR interval; RRm, mean of 256 RR intervals; RRV, variance of 256 RR intervals; SBP, systolic blood pressure; TP, total power; VLF, very-low-frequency.

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INTRODUCTION

Molecular [1] and epidemiological [2] studies have shown that left ventricular hypertrophy associated with arterial hypertension is a risk factor for sudden death. In recent years attention has focused on a predictive index of sudden death based on temporal dispersion of the QT interval (QT), namely the QT variability index (QTVI) [3]. In subjects with structural myocardial disease, including those with dilated cardiomyopathy [3,4] and hypertrophy [5], an increased QTVI is correlated with malignant ventricular arrhythmias. One of the distinctive characteristics of this marker is its dependence on RR interval (RR) variability. Low RR variability is itself another marker of sudden death [6].

Our aim in the present study was to investigate whether the QTVI is influenced by hypertensive cardiomyopathy and by cardiovascular autonomic control. We assessed QTVI in three study groups: hypertensive subjects without vascular complications and with recently observed raised blood pressure levels; patients with hypertrophic cardiomyopathy (HCM) who had received an implantable cardioverter/defibrillator (ICD); and normotensive control subjects. The QTVI was also compared with the slope between QT and RR (QT–RR slope) [7–9], with indices derived from spectral analysis of QT [10] and with measures of QT dispersion [11,12]. Autonomic nervous system function was assessed by power spectral analysis of RR and systolic blood pressure (SBP) variability [6].

METHODS

Study subjects

For this study we selected outpatients who had untreated and uncomplicated mild or moderate hypertension (SBP \( \geq \) 140 mmHg; diastolic blood pressure \( \geq \) 90 mmHg), patients with HCM who had received an ICD, and normal volunteer control subjects from among staff in the clinic (SBP < 140 mmHg; diastolic blood pressure < 90 mmHg). To confirm arterial pressures, subjects in the hypertensive group and the normotensive control group underwent 24 h pressure monitoring. All subjects also underwent 48 h ambulatory ECG monitoring.

Subjects in the hypertensive and control groups were excluded if they had a history or demonstrable evidence of cardiac, vascular, respiratory, renal, liver or gastrointestinal diseases, or electrolyte or metabolic disorders (diabetes, obesity, hypercholesterolaemia).

During echocardiography, data were obtained to determine the left ventricular mass index (LVMI) and ejection fraction. Two-dimensional and M-mode echocardiograms were recorded from standard parasternal and apical windows using a commercially available ultrasound unit (Kontron Instruments). Each variable was measured according to the convention of the American Society of Echocardiography. Echocardiographic left ventricular mass was then calculated from the Penn convention, according to the method described by Devereux et al. [13]. Left ventricular mass was then divided by body-surface area to derive LVMI. Hypertensive subjects with left ventricular hypertrophy were defined as men with LVMI \( > \) 134 g/m\(^2\) and women with LVMI \( > \) 110 g/m\(^2\) [13]. Hypertensive and control group subjects underwent Bruce protocol stress-testing designed to eliminate from the study subjects with silent myocardial ischaemia. Before recordings of RR and arterial pressure variability, 24 h urinary sodium and potassium excretion was measured.

All subjects with HCM had left ventricular hypertrophy of 15 mm or more on two-dimensional echocardiography in the absence of a systemic cause. The HCM patients studied had received an ICD because they had survived a cardiac arrest or syncopal ventricular tachycardia. All ICDs were implanted, after an electro-physiological study, for sustained ventricular tachycardia or ventricular fibrillation. None of the participants was receiving anti-arrhythmic therapy or other drugs that could interfere with autonomic sinus modulation or repolarization phase.

Because a person’s mental state can influence the autonomic nervous system [12,15] and cardiac repolarization [12,15,16], all subjects underwent assessment and scoring for anxiety [12,15–19].

All participants gave their informed consent to the procedures, and the local ethics committee approved the study. The study complied with the ethical rules for human experimentation stated in the Declaration of Helsinki.

Data acquisition

After a 15 min supine rest, each subject underwent a 12-lead ECG recording at a speed of 50 mm/s for the determination of QT dispersion. A 10 min simultaneous recording was then obtained for a single ECG lead (Telemetria Mortara Rangoni), beat-to-beat measurement of arterial pressure (Finapres; Ohmeda) and respiratory rate (strain-gauge belt). During the last few minutes of this recording, subjects were instructed to breathe at 20 breaths/min (0.33 Hz) in time with a metronome. The 256-beat segment recorded under respiratory control was used to determine RR, QT, SBP and respiratory rate.

The three analogue signals (ECG, SBP and respiratory rate) were acquired simultaneously and converted digitally with a custom-designed card (Keithley Metra-byte; DAS 1200 Series) at a sampling frequency of 500 Hz per channel with 12-bit precision.

For recognition and measurement of RR, QT, SBP and respiratory rate, we used a software program developed in our laboratory and based upon an automated
QT variability spectra in normal subjects (top), in hypertensive subjects (middle) and in subjects with HCM (bottom)
The HF spectral component from 0.292 to 0.389 Hz represents respiratory modulation of QT. The LF spectral component oscillates around 0.1 Hz. A third component slightly above 0 Hz is termed VLF. Note the progressive increase in all components from normotensive subjects to those with HCM. PSD, power spectral density.

Offline power spectral analysis of RR and QT variability
Stationary, 256-beat segments of ECG, blood pressure and respiratory recordings were analysed with an autoregressive algorithm (Figure 1). The power spectral densities of the recordings were computed using an autoregressive algorithm developed in our laboratory and described in detail elsewhere [12,15–17,20]. For each subject, four spectra were recorded simultaneously for four different variables (RR, QT, SBP and respiration). For each spectrum we calculated the following components: total power (TP; the total spectral density), a high-frequency (HF) component (from 0.15 to 0.42 Hz), a low-frequency (LF) component (from 0.03 to 0.15 Hz) and a very-low-frequency (VLF) component (below 0.03 Hz) [9,15,16]. All spectral data for RR variability were transformed into natural logarithms (RR\_lnTP, RR\_lnVLF, RR\_lnLF, and RR\_lnHF) [6]. LF and HF powers of RR variability were also normalized [RR\_LF(n.u.) and RR\_HF(n.u.) where n.u. denotes normalized units] [6], and the ratio of LF to HF powers was calculated (RR\_LF/HF) [6].

We also calculated the coherence function between single spectral components of RR and QT; of RR and SBP; and of RR and respiratory spectra [3,17].

To obtain QTVI from the 256-beat segments recorded, we calculated the means of QT (QT\_m) and RR (RR\_m) and their variances (QT\_v and RR\_v) for the 256 beats. QTVI was then determined using the following formula [3–5,17]:

\[
QTVI = \log_{10}([((QT_m)^2)/((QT_v)^2)]/[(RR_m)/(RR_v)^2])
\]

Linear regression was used to calculate QT–RR\_slope [7–9] (Figure 2).
**Measurement of QT and QTc (QT interval corrected for heart rate) dispersion**

The duration of the QT was measured at each lead of the 12-lead surface ECG for two consecutive cycles. Interval dispersion was calculated by the Perkioimaki method [11,12]. Inter-observer measurement error was avoided by using measurements made by the same trained operator. Intra-observer and measurement errors of QT’ and QTc dispersion were defined.

**Data and statistical analysis**

All data were evaluated by the use of the SPSS-PC+ database (SPSS-PC+ Inc., Chicago, IL, U.S.A.). All results are expressed as means ± S.E.M. Participants were initially divided into three groups: subjects with arterial hypertension, patients with HCM and normotensive control subjects. The hypertensive group was subdivided into two groups: with and without left ventricular hypertrophy.

One-way ANOVA was used to compare the general characteristics, QT data (QT, QT dispersion, QT–RRslope, QTVI) and RR spectral data [RRlnLF, RRlnHF, RRtlnLF(n.u.), RRtlnHF(n.u.) and RRtlnLF/HF] in the three groups.

Because spectral data for QT variability expressed in the absolute form have a non-linear distribution, we used the Kruskal–Wallis and Mann–Whitney tests to compare data statistically. For the same reason, the Spearman correlation coefficient was used to compare QTVI, QT–RRslope and QT spectral data.

Possible associations between LVMI and other variables were studied in the hypertensive and normotensive groups using multiple logistic regression analysis. This statistical approach made it necessary to subgroup the hypertensive and normotensive groups according to the presence or absence of left ventricular hypertrophy. A P value of < 0.05 was considered to indicate statistical significance.

**RESULTS**

Of the 162 subjects initially selected for study, 83 (56 males and 27 females) met the inclusion criteria; 23 were excluded because pressure monitoring failed to confirm the required arterial pressures (19 of these had diabetes, 9 were obese and 13 had a positive exercise test).

The general characteristics (including sex, age, body mass index, degree of anxiety, lipids, glycaemia and electrolytes) were similar in the three groups (Table 1). Of the six patients in the HCM group, one belonged to NYHA (New York Heart Association) functional class I, four to class II and one to class III.

Arterial pressures and heart rate were significantly higher in the hypertensive group (P < 0.001). Urinary sodium and potassium excretion was similar in three groups of subjects. The LVMI was larger in the hypertensive than in the normotensive subjects (133 ± 3 g/m² and 105 g/m² respectively; P < 0.001). Of the 44 hypertensive subjects, 30 (22 males and eight females) had ventricular hypertrophy according to the study criteria (LVMI 144 ± 3 g/m²) (see Methods section) and 14 (10 males and four females) did not (LVMI 111 ± 5 g/m²; P < 0.001). The ejection fraction was significantly lower in the hypertensive group than in normotensive control subjects (58 ± 1% compared with 72 ± 1%; P < 0.001).

In HCM subjects, mean left atrium size, left end-diastolic and end-systolic diameters, and maximal left ventricular wall thickness were 44 ± 4 mm, 43 ± 2 mm, 27 ± 2 mm, 31 ± 2 mm respectively. Two patients had left ventricular outflow tract gradients of > 30 mmHg, and two had values of > 60 mmHg.

QT and QTc dispersion were greater in patients with HCM than in the hypertensive and normotensive groups (QT dispersion, 75 ± 3, 33 ± 2 and 25 ± 2 ms respectively (P < 0.001); QTc dispersion, 75 ± 3, 38 ± 2 and 27 ± 2 ms respectively (P < 0.001)). Both hypertensive groups had significantly greater values for QT and QTc dispersion than normotensive subjects (P < 0.001).

All HCM subjects had bouts of non-sustained ventricular tachycardia (three or more consecutive ventricular extrasystoles with a mean rate > 120 beats/min for less than 30 s) during 48 h ambulatory electrocardiographic monitoring. One subject had 10 runs and a second subject had seven runs; the remaining four patients had two runs each. No hypertensive or control subjects showed important ventricular or supraventricular arrhythmias.

**QT spectral data, QTVI and QT–RRslope**

All the spectral indices of QT variability analysed in absolute units (QT, QTc) and QT–RRslope in the hypertensive group were significantly higher than in the normotensive group, but were lower than those of the HCM group (Table 2). The four QT indices were significantly higher in patients with HCM than in normal controls (Table 2). When the indices were transformed into n.u., the only significant differences found were between patients with HCM and normotensive subjects; in particular, the HCM group had significantly higher QTlnLF(n.u.) (P < 0.05) and significantly lower QTlnHF(n.u.) (P < 0.05) than normotensive subjects (Table 2). QT–RRslope coherence were lower in the hypertensive and HCM groups than in the normotensive group (Table 2).

QTVI was significantly higher in hypertensive subjects (−0.71 ± 0.07) than in normotensive controls (−1.27 ± 0.04; P < 0.001), but was significantly lower in hypertensive subjects than in patients with HCM.
Table 1  Baseline characteristics of study subjects

Data are expressed as means ± S.E.M. Significance of differences between groups: *P < 0.05, **P < 0.001 for hypertensive subjects compared with HCM; †P < 0.01 for hypertensive subjects compared with control subjects (ANOVA and Bonferroni test). Listed P values refer to the total significance of differences (ANOVA) among the three groups; NS, not significant. DBP, diastolic blood pressure.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertensive subjects (n = 44)</th>
<th>HCM subjects (n = 6)</th>
<th>Control subjects (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>32:12</td>
<td>3:3</td>
<td>21:12</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ± 1</td>
<td>37 ± 6</td>
<td>47 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 0.5</td>
<td>25 ± 0.4</td>
<td>25 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Anxiety symptom (Kawachi scale score)</td>
<td>1.4 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>1.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Triacylglycerols (mg/dl)</td>
<td>103 ± 8</td>
<td>100 ± 1</td>
<td>100 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>198 ± 6</td>
<td>200 ± 3</td>
<td>181 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Glycaemia (mg/dl)</td>
<td>141 ± 2</td>
<td>141 ± 2</td>
<td>142 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma potassium (mmol/l)</td>
<td>4.2 ± 0.2</td>
<td>4.2 ± 0.1</td>
<td>4.3 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 1*††</td>
<td>80 ± 3</td>
<td>60 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140 ± 3***††</td>
<td>120 ± 3</td>
<td>112 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>86 ± 1**†††</td>
<td>70 ± 1</td>
<td>73 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP 24 h (mmHg)</td>
<td>143 ± 1†††</td>
<td>–</td>
<td>114 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP 24 h (mmHg)</td>
<td>85 ± 1†††</td>
<td>–</td>
<td>76 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate 24 h (beats/min)</td>
<td>72 ± 1†††</td>
<td>–</td>
<td>61 ± 1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2  QT variability data in the study sample

Data are expressed as means ± S.E.M. Significance of differences between groups: *P < 0.05, **P < 0.001 for hypertensive subjects compared with HCM; †P < 0.01 for hypertensive subjects compared with control subjects; †P < 0.05, ††P < 0.001 for subjects with HCM compared with control subjects (normalized QT, coherence, QTVI and QT–RR coherence, ANOVA and Bonferroni test; TP, VLF, LF and HF functions, Kruskal–Wallis and Mann–Whitney tests). Listed P values refer to the total significance of differences (ANOVA) among the three groups; NS, not significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive subjects (n = 44)</th>
<th>HCM subjects (n = 6)</th>
<th>Control subjects (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT₉₀ (ms)</td>
<td>352 ± 5**</td>
<td>486 ± 12††</td>
<td>350 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉ (ms²)</td>
<td>40 ± 5**††</td>
<td>161 ± 6†††</td>
<td>14 ± 1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉² (ms²)</td>
<td>9.8 ± 1.5**†††</td>
<td>47.1 ± 2.5†††</td>
<td>4.4 ± 0.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉₉ (ms²)</td>
<td>11.7 ± 2.1†††‡</td>
<td>51.8 ± 2.0†††</td>
<td>3.9 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉ (ms)</td>
<td>0.09 ± 0.001</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>QT–RR₉₉₉₉ coherence</td>
<td>0.65 ± 0.02†</td>
<td>0.58 ± 0.01†††</td>
<td>0.72 ± 0.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉ (ms²)</td>
<td>18.6 ± 2.9†††‡</td>
<td>62.1 ± 2.0†††</td>
<td>5.8 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉ (Hz)</td>
<td>0.32 ± 0.001</td>
<td>0.33 ± 0.001</td>
<td>0.33 ± 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>QT–RR₉₉₉₉ coherence</td>
<td>0.60 ± 0.02†</td>
<td>0.56 ± 0.01†††</td>
<td>0.67 ± 0.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT₉₉₉₉ (ms)</td>
<td>38.2 ± 2.1</td>
<td>45.5 ± 1.7†</td>
<td>34.0 ± 2.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>QT₉₉₉₉ (ms)</td>
<td>61.8 ± 2.1</td>
<td>54.5 ± 1.7†</td>
<td>65.9 ± 2.3</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

(–0.29 ± 0.04; P < 0.05) (Figure 3). Patients with HCM had a significantly higher QTVI than normotensive subjects (P < 0.001) (Figure 3). No difference was found for QT–RR_slope between hypertensive subjects and normotensive controls, but both groups had a significantly lower QT–RR_slope (P < 0.001) than patients with HCM (hypertensive group, 0.04 ± 0.01; normotensive group, 0.02 ± 0.001; patients with HCM, 0.14 ± 0.07) (Figure 3).

QTVI and QT–RR_slope correlated significantly with QT₉₉₉₉, QT₉₉₉₉², QT₉₉₉₉¹, QT₉₉₉₉² and QT₉₉₉₉³ (Table 3). Also, QT and QTC dispersion both correlated significantly with QTVI, QT–RR_slope, QT₉₉₉₉, QT₉₉₉₉² and QT₉₉₉₉³ (Table 3). Intra–observer variability was 9 ms for QT and QTC dispersion.

**RR and SBP variability**

Hypertensive subjects had significantly lower values than normotensive controls for RR₉₉₉₉ (7.0 ± 0.1 and 7.5 ± 0.1 respectively; P < 0.05), RR₉₉₉₉ (5.6 ± 0.2 and 5.5 ± 0.2 respectively; P < 0.05) and RR₉₉₉₉ (33 ± 3 and 50 ± 2 respectively; P < 0.05), but significantly greater values for RR₉₉₉₉ (3.8 ± 0.5 and 1.8 ± 0.2 respectively; P < 0.05) (Figure 3) and RR₉₉₉₉ (66 ± 3
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Figure 3 Differences in QTVI (top), QT–RR slope (middle) and LF/HF (bottom) in subjects with hypertension, subjects with HCM and control subjects

The central line represents the median distribution; each box spans from 25 to 75 percentile points, and error bars extend from 10 to 90 percentile points (ANOVA and Bonferroni test).

Table 3 Spearman correlations among QT spectral and non-spectral data

<table>
<thead>
<tr>
<th></th>
<th>QT dispersion</th>
<th>QT&lt;sub&gt;T&lt;/sub&gt; dispersion</th>
<th>QTVI</th>
<th>QT&lt;sub&gt;tp&lt;/sub&gt;</th>
<th>QT&lt;sub&gt;vLF&lt;/sub&gt;</th>
<th>QT&lt;sub&gt;vHF&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.74</td>
<td>0.63</td>
<td>0.44</td>
<td>0.41</td>
<td>0.43</td>
<td>0.35</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Figure 4 Differences in QTVI in normotensive subjects and in hypertensive subjects with and without ventricular hypertrophy

The central line represents the median distribution; each box spans from 25 to 75 percentile points, and error bars extend from 10 to 90 percentile points (ANOVA and Bonferroni test).

in the other two groups. The HCM group showed a lower RR<sub>L/F/HF</sub> than hypertensive subjects (Figure 3).

Left ventricular hypertrophy

All spectral indices of QT variability expressed in absolute units (QT<sub>TP</sub>, QT<sub>vLF</sub>, QT<sub>vHF</sub>, QT<sub>HF</sub>, QT<sub>vLF</sub>) were significantly higher in the hypertensive subgroup with left ventricular hypertrophy than in both normotensive control subjects (P < 0.001) and hypertensive subjects without left ventricular hypertrophy (P < 0.001).

The hypertensive subgroup with left ventricular hypertrophy had a significantly greater QTVI (0.10 < 0.05) than both the hypertensive subjects without hypertrophy (0.05 < 0.05) and the normotensive group (0.05 < 0.05; P < 0.001) (Figure 4).

The hypertensive subgroup without hypertrophy also had a significantly larger QTVI than normotensive
control subjects ($P < 0.05$) (Figure 4). No difference was found among these three groups for QT–RRslope.

The same statistically significant differences found for RRTP, RRLP, RRHF, RRLF/HF, RRLP/(n.u.) and RRHF/(n.u.) between the hypertensive and normotensive groups were confirmed for the hypertensive subgroups with and without left ventricular hypertrophy.

Multiple logistic regression disclosed a significant association of left ventricular hypertrophy with RRTP and with QTVI (RRLF/HF, slope = 0.24 (S.E.M. 0.11), $P < 0.05$; QTVI, slope = 4.06 (S.E.M. 0.99), $P < 0.0001$; intercept, slope = 2.40 (S.E.M. 0.96), $P < 0.05$; $\chi^2$ = 38.8; $P < 0.0001$). The other variables were excluded from the equation.

**DISCUSSION**

The data from our present study confirm that people at high risk of sudden death, including patients with HCM who have received an ICD, have an increased QTVI [3–5]. The hypertensive group that we studied – a category at higher risk of sudden death than their normotensive counterparts, although admittedly at lower risk than patients with HCM and an ICD – had intermediate QTVI values. Hence QTVI seems able to stratify the risk of sudden death among the various groups. Conversely, the QT–RRslope, despite being highest in patients with HCM and ICD and higher in the hypertensive than in the normotensive group, did not differ significantly among these categories. QT–RRslope therefore seems less effective than QTVI in highlighting the degree of risk. It could have failed because although we studied a sufficient number of QTs (256) for an analysis of QTVI, we studied too few for analysis of QT–RRslope. Reported studies nevertheless also included data from short-term recordings [6–8]. Whatever the explanation, QTVI seems a more efficient indicator than QT–RRslope for stratifying various categories according to the risk of sudden death.

The QTVI findings received confirmation from the QT spectral data, showing that the spectral components of QT in the hypertensive group were higher than those of normotensive subjects, but lower than those of patients with HCM. In addition, QTVI and the spectral data for QT are interdependent, because QTTP = the sum of all the spectral components – numerically equals QTVI, the variable used to determine QTVI (see the Methods section).

The positive association of left ventricular hypertrophy with QTVI, detected by multiple regression, raises the intriguing possibility that hypertrophy has a determining role in altering QTVI. The greater left ventricular mass could increase both the duration and variance of the QT. Our data suggest that, as well as causing the QT to widen spatially (increased QT dispersion in the 12 leads), these hypertrophic changes in the architecture of the myocardium can also increase autonomic and non-autonomic QT oscillations. Accordingly, in subjects with left ventricular hypertrophy, the duration of cardiac repolarization – measured on the ECG as the QT – is the temporal sum of all myocardial cell repolarizations. The greater the ventricular mass, the lower is the synchronization of repolarization in the single myocardial cells. This phenomenon increases the duration and variance of the QT. At the molecular level, hypertrophy increases the cytoplasmic release of Ca$^{2+}$ by the sarcoplasmic reticulum, with an increase in Na/Ca exchange activity and a non-homogeneous increase in myocardial cell action potentials [1,21]. Again, this asynchrony increases the duration and variance of QT. These cellular and molecular events only partly explain the increased QTVI in our hypertensive groups (Figure 4), because the subgroup without left ventricular hypertrophy also had an abnormally high QTVI. We can clarify this pattern from an arithmetical as well as a physiopathological standpoint. Arithmetically, we attribute the increased QTVI to the decrease in the denominator of the ratio that it generates. This decrease arises from the low RR (see the formula in the Methods section). In addition, the shorter mean RR duration owing to the higher heart rate in hypertensive subjects (see Table 1) fails to balance the reduced RRTP. Hence the denominator tends to diminish, whereas the QTVI increases. Needless to say, low RR variability expressed in terms of variance or other indices is also among the risk factors for sudden death [9].

Compared with the normotensive subjects, the physiological pattern in the hypertensive subjects that we studied was characterized by an increased heart rate, reduced variance (RRTP), increased RRLF/HF and RRLP/(n.u.) and reduced RRHF/(n.u.). This clinical picture is associated with increased sympathetic modulation of the sinus node or with vagal withdrawal, or both events. Hence another explanation for the increased QTVI in the hypertensive subgroup without left ventricular hypertrophy could be their specific autonomic pattern, namely increased sympathetic and reduced vagal control. This autonomic pattern is also characterized at the molecular level by a rise in cytoplasmic Ca$^{2+}$ [22,23] with increased action potentials, accompanied by increased QT duration [22,23] and increased QT variance – two factors favouring arrhythmogenicity [1,21–23]. Accordingly, besides the severity of left ventricular hypertrophy, the other variable associated in multiple regression analysis with the QTVI was RRLF/HF, an index of increased sinus sympathetic and reduced vagal modulation.

What remains unclear is how autonomic sinus control influences cardiac repolarization and power spectral analysis of QT variability. Indeed, the increased QT variance depends not on the predominance of an individual spectral component, but on all the components
(see Table 2). Support for this conclusion comes from the similar data for the normalized spectral components in the hypertensive and normotensive groups. In other words, the relationship among the various spectral components of the QT remains proportionally similar among the various groups, whereas autonomic modulation of the sinus node differs, at least in hypertensive and normotensive subjects. The hypertensive group showed an increase in RR_{LF/HF} and variations in the normalized indexes [RR_{LF(n.u.)} and RR_{HF(n.u.)}] that indicate a sympathovagal imbalance. The spectral components of RR and QT, however, are partly independent. Accordingly, the measure of the interdependency between RR and QT variability, i.e. coherence, tended to diminish significantly in the hypertensive group and in patients with HCM who had received an ICD. This distinction indicates that QT oscillations in subjects with hypertension and primitive HCM originate less from autonomic control and more from a stochastic increase triggered by an action potential asynchrony secondary to structural myocardial changes. Hence, despite their marked effect on RR variability, autonomic nervous system fluctuations contribute less decisively to QT oscillations, as others have observed [10].

A final point to underline is the normal or pseudonormal [24,25] RR_{LF/HF} value that we found in the HCM group. Although in an earlier study Counihan et al. [26] observed the same result in HCM subjects who experienced resuscitated ventricular fibrillation or sudden death, we believe that we studied too few HCM subjects to make a conclusive evaluation.

The significant correlation that we found between QTVI and QT dispersion contrasts with the lack of correlation reported in the original QTVI study conducted by Berger et al. in 1997 [3]. These investigators reported unusually high QT dispersion values in normal subjects, but extremely low values in patients with dilated cardiomyopathy [3]. They described the method used for calculating the two variables only in brief, however, referring the reader to the references for further details. Unfortunately, the method used for calculating QT dispersion, an index that gained favour in the 1990s, varies from study to study. Our data correspond most closely with those reported by Perkioimaki et al. in 1995 [11], from whom we derived the calculations used in the present study. Discrepancies could arise from non-simultaneous recording in the 12 leads, the influence of respiratory activity, or the paper running speed (in the present study, 0.50 cm/s rather than 0.25 cm/s).

In conclusion, patients with arterial hypertension with or without left ventricular hypertrophy have an abnormally high QTVI, probably linked to the autonomic pattern. The significant increase in this index, especially in hypertensive subjects with left ventricular hypertrophy, and its positive relationship with LVMi suggests that hypertrophy plays a primary role in raising the QTVI. Future studies might usefully be planned to compare antihypertensive drugs that can reduce left ventricular mass, and to investigate whether reducing left ventricular mass might lower the QTVI and thus improve outcome.

REFERENCES

14. Reference deleted

Received 20 June 2001/28 September 2001; accepted 15 November 2001