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# Left Ventricular Hypertrophy in Hypertensive Patients Is Associated With Abnormal Rate Adaptation of QT Interval

JAGMEET P. SINGH, MD, DM,* JIM JOHNSTON, BSc, PETER SLEIGHT, MD, FRCP, FACC, ROSEMARY BIRD, BSc, KATHRYN RYDER, MRCP, DPhil, GEORGE HART, DM, FRCP

*Oxford, England, United Kingdom*

***Objectives.*** **This study sought to examine whether the responses of the QT interval to changes in the heart rate were altered in left ventricular hypertrophy (LVH).**

***Background.*** **The QT interval has been shown to have a delayed adaptation to sudden changes in heart rate in normal subjects. Abnormalities in the adaptation of the QT interval to changes in the RR interval may facilitate the development of ventricular arrhythmias.**

***Methods.*** **Consecutive newly diagnosed hypertensive subjects, not taking any medications, were age and gender matched for LVH (n = 21) versus no LVH (n = 16). QT interval dynamics were analyzed under visual control using a validated algorithm with automatic QT measurements at the end of the T wave. A computerized Holter system was developed to study the QT interval response to changes in the RR interval. The adaptive response of the QT interval was measured as the ratio of the slope from 10% to 90% of the QT change relative to the RR interval change ($dQT/dRR_{10-90}$). Steady state adaptation was also studied as the percent shortening and lengthening of the QT interval during acceleration and deceleration of heart rate.**

***Results.*** **The adaptive response of the QT interval measured as $dQT/dRR_{10-90}$ was increased in the LVH group compared with that in the control subjects during both acceleration (0.33 ± 0.06 vs. 0.18 ± 0.02, p = 0.02) and deceleration phases (0.23 ± 0.04 vs. 0.16 ± 0.02, p = 0.03). In the LVH group, the percent lengthening of the QT interval was greater (7.6 ± 0.7 vs. 5.1 ± 0.2, p = 0.03), whereas the percent shortening was not significantly different (5.71 ± 0.5 vs. 4.6 ± 0.3, p = 0.43), than that in control subjects.**

***Conclusions.*** **The QT interval response to changes in the RR interval is rapid and exaggerated in LVH. These abnormalities of the QT interval response demonstrate that there are altered repolarization dynamics in patients with LVH that may make them vulnerable to serious ventricular arrhythmias.**

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Left ventricular hypertrophy (LVH) is a frequent and early manifestation of cardiac structural adaptation in patients with hypertension (1,2). Several prospective studies (3–5) have clearly demonstrated that LVH represents a risk factor for cardiovascular morbidity and mortality, including sudden cardiac death. This increased risk is independent of the impact of high blood pressure and other risk factors on the cardiovascular system (6). Although there is an increased prevalence and severity of ventricular arrhythmias associated with LVH, the electrophysiologic mechanisms by which it is linked to increased mortality have not been clearly documented.

Because all arrhythmogenic processes include alterations of the action potential, QT interval measurements that represent ventricular repolarization may help to identify abnormal electrophysiologic behavior in LVH. The QT interval varies continually, conditioned by changes in heart rate, autonomic nervous system and loading effects (7,8). The latter two are altered in LVH; hence, the rate-dependent changes in the QT interval in LVH are likely to differ from those in normal hearts. The presence of steady state differences in the duration and regional dispersion of the QT interval in patients with LVH versus normal subjects (9) suggests that there may also be differences in rate-dependent properties.

The QT interval has been shown (10,11) to have a delayed adaptation to sudden changes in heart rate in normal subjects. It is conceivable that abnormalities in the rate-dependent adaptation of the QT interval may facilitate the development of ventricular arrhythmias. The object of the present study was to examine whether this rate-adaptive response of the QT interval is altered in LVH. We also examined the hypothesis that the physiologic changes in heart rate had a greater influence on QT interval duration in patients with LVH than in normal subjects.

## Methods

**Study subjects.** Forty-four consecutive subjects recruited from the hypertension clinic of the John Radcliffe Hospital

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*Present address and address for correspondence: Dr. Jagmeet Singh, Framingham Heart Study, 5 Thurber Street, Framingham, Massachusetts 01701. E-mail: jagmeet@fram.nih.nhlbi.gov.


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**Abbreviations and Acronyms**

| | | |
|---|---|---|
| dQT/dRR | = | relative rate of QT change in reponse to change in RR interval |
| $dQT/dRR_{10-90}$ | = | ratio of slope from 10% to 90% of QT change relative to change in RR interval |
| ECG | = | electrocardiogram, electrocardiographic |
| LVH | = | left ventricular hypertrophy |
| SD-QT | = | standard deviation of consecutive uncorrected QT intervals over 24-h period |

were studied prospectively. Patients were included after a detailed history, physical examination and electrocardiogram (ECG). Recent laboratory reports of their serum electrolyte levels were reviewed. Subjects with evidence of angina, old myocardial infarction, valvular heart disease, congestive heart failure, diabetes mellitus, renal failure, atrial fibrillation, left bundle branch block and pacemaker implantation were excluded from the study. All subjects were under investigation for hypertension and had undergone 24-h ambulatory blood pressure monitoring before recruitment. Echocardiography was performed to assess left ventricular mass and fractional shortening, after which patients underwent 24-h ambulatory ECG monitoring. No secondary causes of hypertension could be elicited in any subject.

Twenty-five patients were observed to have LVH versus 19 who had normal left ventricular wall thickness (control subjects). All subjects were recently diagnosed with hypertension and were not started on any medication until after completion of the Holter recording. All subjects were instructed to abstain from exercise, caffeine and alcohol during the 24-h Holter recording. The protocol was approved by the Central Oxford Regional Ethical Committee, and written informed consent was obtained from all subjects.

**Holter system and QT interval measurement.** A computerized Holter system was used to measure the QT interval over 24 h. ECG leads $V_2$ and $V_5$ were recorded for 24 h on a cassette recorder (Datrix, XR-300). The Holter tapes were replayed at 200 times the recording speed into a programmable waveform analyzer (Century Color Trace Model, Biomedical Systems). The ECG was digitized at a sampling rate of 400 Hz, with the QRS signals detected by a template-matching algorithm. The working algorithm for QT interval measurement involved a rate-dependent search window to locate the T wave peak, after which the point with the steepest slope along the descending limb of the T wave and area of least variation were identified. The end of the T wave was defined as the point where the maximal negative slope intersected the baseline. The channel with the most suitable T wave amplitude and configuration was selected for analysis, with the QT interval measured in a semiautomated and interactive manner under operator control. Markers for onset of the QRS complex and the end of the T wave could be reset by altering the algorithm variables and rescanning the relevant segments whenever required. A moving average of 10 beats was used to improve signal quality and in turn to allow more accurate identification of the end of the T wave. Time intervals were resolved to 2.5 ms. Segments that showed abrupt heart rate changes were identified from the trends and were edited again with extra care. Artifacts and supraventricular and ventricular ectopic beats were excluded from the analysis. All measured values were stored in ASCII format and subsequently converted to a binary format, from which all subsequent calculations were made.

For a tape/patient to be satisfactory for this study, the Holter recording had to have a noise-free baseline, no conduction disorder and a T wave with amplitude >50 $\mu$V. Three tapes in the control group and four in the LVH subset were excluded from the study because of these criteria.

**Rate adaptation of QT interval.** Rate adaptation of the QT interval was measured as the relative rate of change in the QT interval in response to a change in the RR interval (dQT/dRR). We studied this adaptation for both accelerations and decelerations in heart rate during the daytime. After identification of the acceleration or deceleration segments from a graphic projection of the acquisition file, the QT and RR intervals trends were smoothed by a 25-beat filter. A minimal QT change of 25 ms was required for a segment to be considered suitable for the study. The QT and RR interval slopes were measured between 10% and 90% of the change in the intervals after determining the mean QT and RR values over 10 beats at the beginning and end of the test segments (Fig. 1). The ratio of the slopes of the two intervals ($dQT/dRR_{10-90}$) was calculated. An average of three segments were studied during the awake period in each patient.

**Percent change in QT interval.** QT adaptation was also studied as the percent decrease and increase in the QT interval for each 100-ms shortening or lengthening of the RR interval during acceleration and deceleration of the heart rate, respectively. The QT interval at the shortest and longest RR intervals and at as many other cycle lengths as possible were selected in each patient. To adjust for differences in baseline values of the QT interval, we expressed the adaptation of the QT interval to heart rate changes as the percent of QT change; the difference in the QT intervals divided by the difference between the respective RR intervals multiplied by 100 (12). This index describes the percent shortening or lengthening of the QT interval for each 100-ms decrease or increase in the RR interval.

**QT-RR index.** Each QT interval was divided by its respective RR interval, generating a histogram separately for the daytime and nighttime periods. The QT-RR index was expressed as the mean value and standard deviation of the QT/RR value. The maximal and minimal ranges of this index were also examined in the two groups.

**SD-QT and QT/heart rate slope.** Temporal dispersion of the QT interval over a 24-h period was measured as the standard deviation of consecutive uncorrected QT intervals over a 24-h period (SD-QT). Rate-dependent changes in the QT interval were also studied as a function of the QT/heart

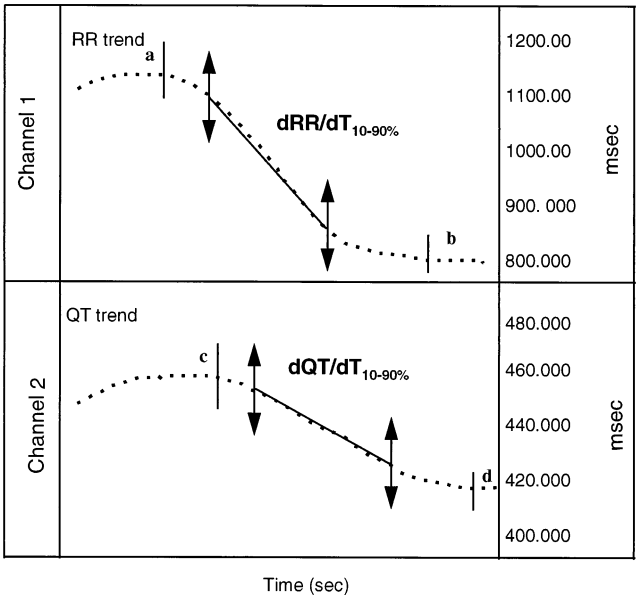



**Figure 1.** Simulated acceleration segment as seen on the acquisition file. Channels 1 and 2 show the RR and QT interval trends. Point *a* marks the initiation of change and point *b* the stabilization of the RR interval. Point *c* represents the onset of change in the QT interval, whereas point *d* marks its stabilization. $dQT/dT_{10-90\%}$ and $dRR/dT_{10-90\%}$ are calculated as the slopes between 10% and 90% of change in the respective intervals. These are represented by the segment between the two **arrowheads.** The relative rate of change of the QT interval is calculated as the ratio of these two slopes ($dQT/dRR_{10-90\%}$).

rate slope, which was derived from regression analysis of the QT intervals with respect to heart rate over 24 h.

**Echocardiography.** Two-dimensional guided M-mode echocardiography was performed with standard techniques by a single operator (J.P.S.) who had no knowledge of the surface ECG and blood pressure readings. Left ventricular end-diastolic dimensions and posterior wall and septal wall thicknesses were measured with use of the Penn convention (13). Left ventricular mass was calculated by the anatomically validated formula of Devereux and Reicheck (14) and left ventricular mass index by dividing left ventricular mass by body surface area. Echocardiographic LVH was diagnosed when left ventricular mass index exceeded 131 $g/m^2$ in men and 108 $g/m^2$ in women (14).

**Statistical analysis.** Results are expressed as mean value ± SEM. Comparison was made between the two groups using a two-tailed unpaired Student *t* test. A p value $<0.05$ was considered statistically significant.

## Results

**Patient characteristics.** Twenty-one patients with LVH and 16 control subjects were age and gender matched (Table 1). All subjects had mild or moderate hypertension, with comparable blood pressure and ventricular function in both groups. The mean corrected QT interval over a 24-h period was longer in the LVH group than in the control group (439 ± 8 vs. 407 ± 5, p = 0.015).

**Table 1.** Patient Characteristics

| | Control Group (n = 16) | LVH Group (n = 21) | p Value |
|---|---|---|---|
| Age (yr) | 53 ± 4 | 58 ± 3 | 0.15 |
| Men/women | 11/5 | 15/6 | |
| LVMI ($g/m^2$) | 106 ± 4 | 166 ± 10 | 0.0001 |
| LVEF | 0.64 ± 0.3 | 0.66 ± 0.5 | 0.67 |
| QTc interval (ms) | 407 ± 5 | 439 ± 8 | 0.015 |
| RR interval (ms) | 833 ± 27 | 858 ± 28 | 0.67 |
| SBP (mm Hg) | 155 ± 6 | 158 ± 4 | 0.59 |
| DBP (mm Hg) | 95 ± 2 | 99 ± 2 | 0.18 |

Data presented are mean value ± SEM or number of patients. DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; QTc = corrected QT interval; SBP = systolic blood pressure.

**Prevalence of ventricular arrhythmia.** Nineteen percent of patients with LVH had a mean ventricular premature beat frequency >10/min. Two of these subjects had a single episode of nonsustained ventricular tachycardia with a run of 4 beats. No significant arrhythmias were seen in subjects without LVH.

**Rate adaptation of QT interval.** The QT interval response to heart rate changes was markedly different in the group with LVH. The adaptive response of the QT interval ($dQT/dRR_{10-90}$) was faster during both acceleration (0.33 ± 0.06 vs. 0.18 ± 0.02, p = 0.02) and deceleration (0.23 ± 0.04 vs. 0.16 ± 0.02, p = 0.03) of heart rate in the LVH group than in the control group (Fig. 2). There was no significant difference in RR interval duration before the onset of heart rate change between the two groups during both acceleration (839 ± 22 vs. 818 ± 24 ms, p = 0.19) and deceleration (668 ± 15 vs. 683 ± 17, p = 0.41).

**Percent change in QT interval.** The amplitude of response to an abrupt decrease in heart rate was different in the two groups. Figure 3 shows the individual responses and averages for the two groups during both an increase and decrease in heart rate. In response to decreases in heart rate, the QT interval was longer in the LVH group than that in the control group (7.26 ± 0.6 vs. 4.99 ± 0.4, p = 0.002 [percent increase in QT interval/100-ms lengthening of RR interval]). The extent of shortening of the QT interval in response to an acceleration in heart rate was not different from that in the control group (5.11 ± 0.5 vs. 4.6 ± 0.35, p = 0.43).

**QT-RR index.** There was no significant difference in mean QT-RR index between the two groups. However, significant circadian differences were observed within the groups during the sleep and awake periods (Table 2).

**Temporal dispersion of QT interval (SD-QT).** SD-QT was greater in the LVH group than in the control group (33 ± 2 vs. 22 ± 1 ms, p = 0.002). However, the correlation between the extent of variability and left ventricular mass index was weak (r = 0.38, p = 0.019) (Fig. 3).

**QT/heart rate slope.** The QT/heart rate slope was steeper in the LVH group than in the control group (−2.2 ± 0.16 vs. −1.77 ± 0.09, p = 0.03).

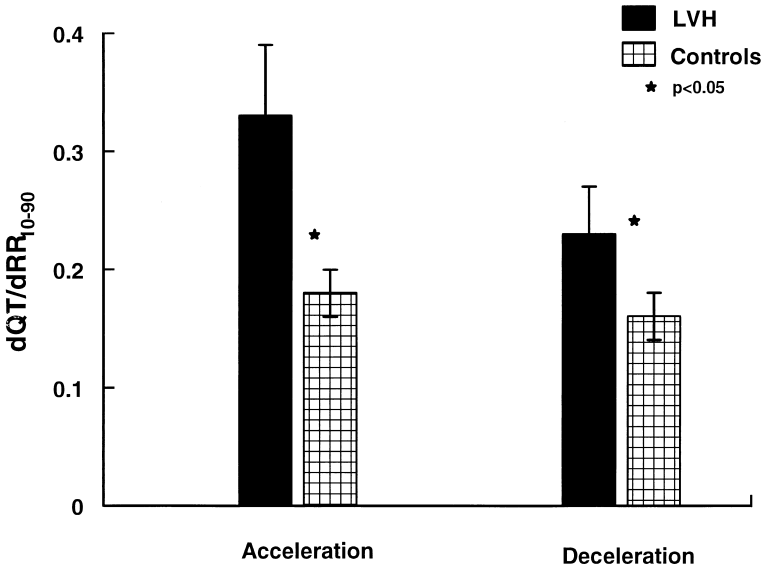
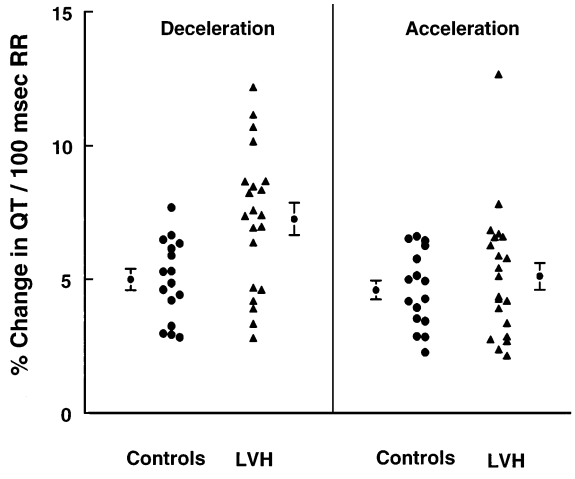



**Figure 2.** Summary of the results of the QT interval adaptive response. The adaptation of the QT interval is faster during both acceleration and deceleration of heart rate in the LVH group than in the control group.

## Discussion

The results of the present study showed that adaptation of the QT interval to changes in heart rate is different in hypertensive patients with LVH than in those with a normal ventricular wall thickness. The adaptive response was more rapid in patients with increased left ventricular mass. The extent of change in the QT interval with changes in heart rate was also more marked in the LVH group. The QT interval lengthened more markedly in the group with LVH on deceleration of heart rate. The QT/heart rate slope was steeper and the temporal dispersion of the QT interval greater in patients with LVH than in the control subjects.

**Figure 3.** Percent change in QT interval for each 100-ms change in RR interval during both acceleration and deceleration, showing individual data points for each patient. Mean percent lengthening of the QT interval during deceleration is greater in the LVH group than in the control group, although the lengthening response of the QT interval in 12 patients overlaps that of the control group. The percent shortening of the QT interval during acceleration in the LVH group is similar to that in the control group.




The arrhythmogenic substrate in LVH has to do with reentry mechanisms due to fibrillar stretching and anisotropy, as well as with self-sustaining activity triggered by afterpotentials that depend on the activation of slow calcium channels (15). It is probable that these differences in the dynamics of the repolarization segment underlie this enhanced arrhythmogenicity in LVH.

**Effect of changing heart rate.** The shortening of the QT interval in response to an increased heart rate is a fundamental physiologic occurrence that is not instantaneous and is preceded by a time lag (16). The change in QT interval is influenced by both heart rate and autonomic tone, the latter principally determining the heart rate-independent changes (7). This response to an increase in heart rate is also an intrinsic property of the myocardial cell (17). The delayed adaptation of the QT interval to sudden changes in heart rate could be a result of a disturbance in the ionic balance at the cellular level. An increase in heart rate would affect the inward fast $Na^+$ and $Ca^{2+}$ currents, consequently altering both the $Na^+$-$K^+$ exchange pump and $Na^+$-$Ca^{2+}$ exchange activity. Homeostatic mechanisms within the cell would then take a finite time to readjust to the new steady state (18). It could hence be postulated that the differences we observed in the QT adaptive response in LVH could either be a cellular phenomenon resulting from altered behavior of the hypertrophied myocyte or a consequence of an abnormal autonomic, tone as has been described in this condition (19). Similar reasoning

**Table 2.** QT-RR Index in the Two Study Groups

| Group | Daytime (mean ± SEM) | Nighttime (mean ± SEM) | p Value |
|---|---|---|---|
| Control | 0.46 ± 0.01 | 0.49 ± 0.01 | 0.004 |
| LVH | 0.46 ± 0.02 | 0.51 ± 0.02 | 0.005 |

LVH = left ventricular hypertrophy.

would apply to QT interval adaptation on abrupt reductions in heart rate.

**Effect of increasing heart rate.** Recent evidence (20,21) from recordings from automatic implantable cardioverter-defibrillator devices and 24-h ECGs suggests that ventricular tachycardia can be initiated by a reentry circuit resulting from the slowed conduction of a normal sinus beat through an area of diseased tissue with decremental conduction properties. During abrupt heart rate accelerations, the presence of a delay in the adaptive response of the QT interval would protect from this possibility by maintaining the refractoriness of the normal myocardium and preventing its stimulation by the impulse exiting the slow conduction tissue. However, an exaggerated adaptive response of the QT interval to abrupt heart rate changes in the setting of LVH, which is characterized by electrophysiologically silent and slow conducting regions (22), may precipitate reentry and arrhythmias. This hypothesis is consistent with the observations of Fei and Camm (23), who noted increased heart rates and shortened QT intervals preceding spontaneous ventricular tachycardia.

**Effect of decreasing heart rate.** Abrupt deceleration of heart rate in LVH is associated with rapid adaptation and an increased percent lengthening of the QT interval, resulting in increased duration of the repolarization segment in the early adaptive phase of heart rate deceleration. Prolonged repolarization would favor the emergence of both early and delayed afterdepolarizations, leading to triggered ventricular arrhythmias (24).

**Other measures of QT interval dynamics.** Variability of the QT interval measured as SD-QT was increased in the subjects with LVH. This finding represents an enhanced temporal dispersion of the repolarization segment in the LVH subgroup. However, we found poor correlation with left ventricular mass index, implying that QT interval variability was independent of the extent of hypertrophy.

A steeper QT/heart rate slope implies that a change in QT interval duration for a particular change in heart rate is more pronounced in LVH, which, along with an increased temporal dispersion of the QT interval, suggests that the repolarization segment in the setting of LVH is more labile, thereby increasing its vulnerability to develop reentry arrhythmias. This increased vulnerability is further favored by the presence of an appropriate underlying electrophysiologic substrate.

However, the QT-RR index was not significantly different, showing that the range of QT-RR combinations was similar between the two groups, which in turn implies that the duration of the QT interval is not uniquely important for generating arrhythmias but is a dynamic phenomenon. There were significant sleep–awake differences in this index within the two groups, demonstrating the influence of a changing autonomic tone on the QT-RR relation. The mean diurnal difference was exaggerated in the LVH group (Table 1).

**Clinical implications.** Sudden arrhythmic death has been associated with vigorous exertion, with cardiac arrest occurring during or immediately after the exertion or stress (25). The Framingham study (26) found a significant association between the mode of death and activity, with sudden death occurring more frequently in the setting of physical activity. This finding is pertinent to our results because events precipitating sudden death are usually associated with an acceleration or deceleration of heart rate.

Although in the present study the adaptive response of the QT interval was studied in relation to physiologic changes in heart rate, it would seem reasonable to speculate that the changes observed may have been even greater had heart rate alterations in the context of activities associated with abrupt heart rate changes (i.e., sudden strenuous exercise and stress) been studied. An abrupt acceleration of heart rate with a faster QT interval adaptive response might be more likely to precipitate reentry and malignant ventricular arrhythmias in hypertrophied hearts than slower heart rate changes.

Likewise, the enhanced adaptive and lengthening response of the QT interval that occurred during deceleration of heart rate accompanying the immediate postexercise period would result in prolonged repolarization. This period is characterized by vagally induced deceleration of heart rate that occurs in the setting of persistent high sympathetic activity (27). This period has also been characterized by persistent elevations in plasma catecholamine, lactate and free fatty acid levels and rapid decreases in potassium levels (28,29). Animal studies (24) have shown that the longer duration of ventricular action potential in hypertrophied hearts predisposes to the development of early afterdepolarizations that appear to trigger ventricular tachyarrhythmia. Hence a rapid adaptive response of the QT interval resulting in prolonged repolarization in the setting of an abnormal metabolic milieu could favor the emergence of this electrophysiologic event.

Arrhythmias in LVH have an adrenergic profile, occurring more frequently in the context of sympathetic predominance (27). An elevated sympathetic tone in subjects with LVH suggests that an interaction between autonomic tone and substrate sensitivity is the probable cause of the arrhythmias. Whether these differences in the adaptive response are a consequence of a variance in autonomic tone or indicate a role for the hypertrophied myocyte needs confirmation and could have important therapeutic implications in the selection of an antihypertensive agent.

**Study limitations.** In the present study, the control group intentionally included hypertensive, not normal, subjects to focus on the relation between a hypertrophied heart and its QT interval dynamics. Elimination of the influence of hypertension as a confounding variable was important because hypertensive subjects have been shown (30) to have elevated sympathetic tone, which could itself influence the dynamic behavior of the QT interval.

The study patients included those with mild to moderate hypertensive LVH. Further studies are needed in patients with more severe LVH and of different etiologies, before our findings can be extrapolated to the LVH population as a whole. Thus, the results of this research should be considered a working hypothesis requiring further validation.

Our assessment of QT interval dynamics was not entirely

beat to beat because we used a moving average of 10 beats to improve the signal quality to assist us in accurately identifying the end of the T wave. In the acquisition file, the QT and RR trends were further smoothed with a 25-beat filter. Our results need to be interpreted after these technical points are taken into consideration. However, the extent of filtering was constant for both RR and QT intervals and for both groups; hence, any possible influence on the results would be similar in both groups. In an attempt to make our measures of the QT adaptive response more reproducible, we used cutoff points ranging from 10% to 90% of change in QT and RR intervals. Use of these cutoff points could result in the loss of vital information concerning the lag in the adaptive response, which is maximal in the initial period of change in heart rate. Despite this limitation, we obtained differences between the two groups.

Automated systems require T wave heights above a predefined lower limit for accurate identification of the T wave end. The Holter system used was unable to measure the QT interval in beats where the T wave height fell below 50 $\mu$V. Although this is important to accurately determine the end of the wave, there are times when the QT interval is not measured. This was not a limitation of this study because one of the selection criteria was a T wave height $>50$ $\mu$V. Even though there are periods during the 24-h recording when the T wave height drops to $<50$ $\mu$V, the time intervals when this occurs are short and comprise $<10\%$ of the total intervals. All the RR intervals with their corresponding QT intervals are then used to generate their respective trends in the acquisition file, from which measurements of the adaptive response of the QT interval were made. In the segments used to measure the adaptive response if any beat had a T wave amplitude $<50$ $\mu$V, a measured value intermediate to the two adjacent beats was interpolated.

Percent change in QT interval is dependent on factors other than the initiating and terminating RR interval, such as rapidity of the change in heart rate and the prevailing autonomic tone. To overcome this dependence, as many segments as possible during the awake period were studied.

**Conclusions.** Our study shows that the adaptive response of the QT interval to changes in heart rate is increased in LVH. The percent lengthening of the QT interval in response to physiologic changes in heart rate was also greater in the LVH group. An increased temporal dispersion of the QT interval and a steeper QT/heart rate slope suggest an increased lability of the repolarization segment in patients with LVH. These abnormalities in the dynamic behavior of the QT interval could help to explain the electrophysiologic mechanisms by which hypertrophied hearts are linked to sudden arrhythmic death.

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