Combined QT Interval and Voltage Criteria Improve Left Ventricular Hypertrophy Detection in Resistant Hypertension

Gil Salles, Sharon Leocádio, Katia Bloch, Armando R. Nogueira, Elizabeth Muxfeldt

Abstract—QT interval parameters have been associated with left ventricular hypertrophy (LVH) in hypertensive patients. The aim of this study is to assess this relationship in resistant hypertension and, in particular, to evaluate whether any QT interval parameter could provide additive information for LVH beyond that obtained from the best electrocardiographic voltage criterion. In a cross-sectional study, 471 resistant hypertensives were submitted to standard 12-lead ECGs, 24-hour ambulatory blood pressure monitoring, and 2D echocardiographic examinations. QT interval durations and QRS voltages were measured, and maximum rate–corrected QT interval duration (QTc\text{max}) and dispersion (QTd), and Sokolow’s and Cornell’s voltage product were calculated. Statistical analyses involved bivariate tests and multivariate logistic regression, with LVH as the dependent variable. A total of 383 patients (81%) had echocardiographic LVH. In bivariate comparisons, both QT interval parameters showed a predictive performance for LVH similar to Cornell’s product, the best ECG voltage criterion. In multivariate analysis, QT parameters and Cornell’s product were independently associated with LVH, after adjustment for other LVH determinants. QTc interval >440 ms\textsuperscript{1/2} and dispersion >60 ms were associated with a 2-fold (95% confidence interval [CI], 1.1 to 3.8) greater chance of having LVH, whereas Cornell’s product >240 mV\textcdot ms implied a 2.6-fold (95% CI, 1.2 to 6.1) increased chance of LVH. The combination of prolonged QT interval and increased Cornell’s product was associated with a 5.3- to 9.3-fold higher chance of having LVH. Hence, although in isolation, no QT interval parameter performs better for LVH detection than simpler Cornell’s product, it provides additive information and can be used in combination with voltage criteria to refine LVH risk stratification in resistant hypertension. (Hypertension. 2005;46:1207-1212.)

Key Words: echocardiography ■ electrocardiography ■ hypertension, arterial ■ hypertrophy

Resistant hypertension (RH) is defined as uncontrolled office blood pressure (BP) in spite of an optimal regimen with ≥3 antihypertensive drugs at full dosages, always including a diuretic.\textsuperscript{1} It is a clinical condition in which the persistently elevated BP levels frequently lead to the development of target-organ damage and to high cardiovascular morbidity and mortality.\textsuperscript{2} Left ventricular hypertrophy (LVH) is strongly associated with cardiovascular mortality.\textsuperscript{3} Subjects with LVH have an especially high risk of sudden cardiac death, up to several times that of those without LVH.\textsuperscript{4}

Prolonged QT interval duration or dispersion are associated with the occurrence of life-threatening ventricular arrhythmias and thus are presumed to represent potential predictors of increased cardiovascular risk.\textsuperscript{5} In patients with hypertension, QT interval parameters have mainly been associated with left ventricular mass,\textsuperscript{6,7} although 2 studies\textsuperscript{8,9} suggested that they are no better than simple electrocardiographic voltage criteria for LVH detection. Moreover, it has been reported recently that they probably constitute true cardiovascular mortality markers in hypertensive patients.\textsuperscript{10,11} As far as we know, no study has evaluated QT interval parameters in patients with RH, a common but generally understudied subgroup of hypertensive patients.

Therefore, the objective of this study was to assess the relationships between various QT interval–derived parameters and echocardiographic LVH in a large group of RH patients and, particularly, to evaluate whether any QT parameter can provide additive information for LVH detection beyond that obtained from the best ECG voltage criterion.

Methods

Subjects and Baseline Procedures

This was a cross-sectional study with 471 RH patients (27.6% males; mean age 59.9 years [SD 11.7]; mean known duration of hypertension 18.9 years [SD 12.1]) enrolled between January 2000 and September 2004 in the hypertension outpatient clinic of our university hospital. All participants gave written informed consent, and the local ethics committee had approved its protocol previously. The enrollment criteria, baseline protocol, and diagnostic definitions have been detailed previously.\textsuperscript{12,13} In brief, all hypertensives referred who fulfilled criteria for RH (office BP ≥140/90 mm Hg using ≥3 antihypertensive drugs in full dosages, always including a diuretic) were submitted to a standard protocol that included a thorough
clinical examination, laboratory evaluation, 12-lead ECG, 24-hour ambulatory BP monitoring (ABPM), and 2D echocardiography. In clinical interview, demographic and anthropometric characteristics (sex, age, race, weight, height, and waist circumference), cardiovascular risk factors (diabetes, dyslipidemia, smoking, physical inactivity, and obesity) and target-organ damage (coronary heart disease, heart failure, cerebrovascular disease, advanced retinopathy, and peripheral arterial disease) were recorded. BP was measured twice by a trained physician, with patients in the sitting position, using a calibrated mercury sphygmomanometer and a suitably sized cuff. First and fifth Korotkoff’s sounds were the criteria for systolic BP (SBP) and diastolic BP (DBP) and BP considered was the mean between the 2 readings. Laboratory evaluation included fasting glycemia, serum creatinine, and lipid profile. Microalbuminuria, proteinuria, and creatinine were evaluated in a sterile 24-hour urine collection. Abnormal microalbuminuria was considered if ≥30 and ≤300 mg per 24 hours and nephropathy if proteinuria ≥0.5 g per 24 hours or creatinine clearance ≤1 mL/s. ABPM was recorded using Mobil O Graph (version 12) equipment, approved by the British Society of Hypertension. All patients used their prescribed antihypertensive medications during ABPM. A reading was taken every 10 minutes throughout the day and every 20 minutes at night. Parameters evaluated were average 24-hour, daytime, and nighttime SBP and DBP and DBP and nocturnal SDB/DBP reduction. Nighttime period was ascertained for each individual patient from registered diaries. Two-dimensional transthoracic echocardiography (Sonoline G60S; Siemens) was performed by the same experienced observer. Left ventricular mass was calculated by Devereux’s formula and indexed to body surface area (LVMI) and, alternatively, to height. The diagnosis of LVH was defined by LVMI >116 g/m² in men and >104 g/m² in women.

**Electrocardiography**

Standard resting 12-lead ECGs were recorded digitally in the same equipment (CardioFax V ECG; Nihon-Kohden) and response frequencies at 25 mm/s paper speed and 10 mm/mV amplitude. ECGs were 100% amplified on a computer screen, and a single independent observer unaware of other patients’ data measured QRS voltages and QT intervals. The onset of QRS to the peak of T wave, and QT interval (from the onset of QRS to offset of T wave) durations in every lead where possible, using a commercial image software (resolution 0.1 mm=4 ms), as described previously. The end of T wave was defined as the visual return to the TP baseline; when U waves were present, the QT was measured to the nadir between T and U waves. Whenever the offset of T wave could not be identified, the lead was discarded from analysis (a minimum of 8 leads and 4 precordial ones was necessary; the mean number of leads measured was 10.6±1.1 leads per ECG; median 11 leads). Electrocardiographic voltage criteria recorded were Sokolow–Lyon (SV1+RV5 or V6 >3.5 mV), Cornell (SV3+RaVL >2.6 mV with 0.6 mV added in women), and Cornell voltage product (Cornell voltage with 0.6 mV added in women×mean QRS duration >240 mV²·ms). The presence of typical ST-T wave strain pattern (downsloping convex ST segment with inverted asymmetrical T wave opposite to QRS axis in leads V5 and V6) was also recorded. QT interval parameters recorded were maximum rate-corrected (by Bazett’s formula) QTmax, QTend (QTcmax), and JT (calculated as QTcmax×mean QRS durations). Their respective interval dispersions were calculated either as the difference between maximum and minimum interquartile durations (QTd) and also as their variation coefficients (mean/SD×100). To assess QT interval measurement intraobserver reproducibility, 50 randomly chosen ECGs were measured again after 6 months after the first measurement. Mean relative errors were 1.8% for QTcmax and 21% for QTd. The mean intraobserver absolute error for QTcmax was 1.8 ms (SD 11 ms), and for QTc it was 5.2 ms (SD 12.2 ms). This signifies that 95% of the intraobserver variability for QTcmax measurement lied within −16 and +22 ms², and that for QTd within −19 and +29 ms.

**Statistical Analysis**

Continuous data were described as medians and 5% and 95% percentile values. For normally distributed data, confirmed by Kolmogorov–Smirnov test (age, body mass index [BMI], office and ABPM pressures, and Sokolow voltage), bivariate comparisons between patients with and without LVH were performed by unpaired t test and for those asymmetrically distributed by nonparametric Mann–Whitney test. Categorical variables were compared by χ² test. Individual performance of QT interval parameters and ECG voltage criteria for detecting LVH was tested by receiver operating characteristics (ROC) curve analyses, describing areas under curves with their 95% confidence intervals (CIs) and sensitivities at fixed 90% specificity. A multivariate logistic regression with LVH as the dependent variable was performed to assess the independent associations of QT interval parameters (dichotomized at well-known abnormal values) together with ECG voltage criteria, after adjustment for other potentially important variables that could influence LVH (age, sex, race, BMI, waist circumference, diabetic status, lipid profile, microalbuminuric status, 24-hour BPs on ABPM, and electrocardiographic ST-T strain pattern). Results were presented as odds ratios with their 95% CI. Also, to evaluate the complementary information for LVH detection provided by QT parameter and ECG voltage criterion, a combined test variable was derived that incorporated both measures into 3 categories: nonprolonged QT parameter and normal voltage criterion (the reference category), either prolonged QT parameter or increased voltage criterion, and prolonged QT parameter and increased voltage criterion. All statistics were performed by SPSS statistical package version 13.0 and a 2-tailed P value <0.05 was regarded significant for multivariate modeling.

**Results**

**Baseline Characteristics and Comparisons Between Patients With and Without LVH**

A total of 383 RH patients (81%) had echocardiographic LVH. Using LVM indexed to height instead of to body surface area increased LVH prevalence to 87% but did not alter other results. Table 1 shows the baseline characteristics of patients with and without LVH. Patients with LVH were more frequently males of white race and had higher BMI and waist circumference. They had office BPs similar to those without LVH but had increased mean 24-hour, daytime, and nighttime BPs on ABPM. Their therapeutic regimens were similar to those without LVH. Patients with LVH also showed lower serum total and HDL cholesterol and higher urinary albumin excretion. Table 2 shows electrocardiographic variables in patients with and without LVH. All QT interval parameters and ECG voltage criteria, except Sokolow–Lyon, were significantly increased in LVH patients. Because the strongest associations with LVH were observed with maximum rate-corrected QTcmax duration (QTcmax) and QTcmax dispersion (QTd), only these 2 parameters were presented. The prevalence of typical ECG ST-T strain pattern was also higher in patients with LVH.

**Individual Performances of QT Parameters and Voltage Criteria for Detection of LVH**

Table 3 shows the areas under ROC curves and the sensitivities at fixed 90% specificity of QT parameters and ECG voltage criteria for detection of LVH. Cornell voltage product was the best ECG voltage criterion, with a predictive performance slightly better than the 2 QT parameters.
Independent and Complimentary Associations of QT Parameters and Voltage Criteria With LVH

After adjustment for other important covariates that could possibly influence LVMI, QTc\textsubscript{max} prolongation $\geq$440 ms\(^1\) (model A) and increased QTd $\geq$60 ms (model B) were associated with a 2-fold greater chance of having LVH (95% CI, 1.1 to 3.8), whereas increased Cornell product ($\geq$240 mV $\cdot$ ms) was associated with a 2.6-fold greater chance (95% CI, 1.2 to 6.1; Table 4). In combination (Table 5), the presence of prolonged QT parameter (either QTc\textsubscript{max} or QTd) and increased Cornell product was associated with a 5.3- to 9.3-fold greater chance of having LVH compared with the subgroup of patients with normal QT interval and Cornell product. The subgroup with either prolonged QT parameter or increased Cornell product still had a 2-fold greater chance of having LVH.

Discussion

This study has 2 main findings. First, Cornell’s voltage product is, in isolation, the best ECG voltage criterion for...
LVH detection in RH patients with a high prevalence of echocardiographic LVH. Second, the 2 best QT interval parameters (QTcmax and QTd) are no better than Cornell’s voltage product to detect LVH, when used in isolation, but provide additive information for LVH detection and could be used in combination with Cornell’s product to improve LVH risk stratification in this group of patients.

The finding that Cornell’s voltage product was the best ECG criterion for LVH detection has been extensively demonstrated previously.18,19 Increased left ventricular mass has been associated separately with QRS amplitude and duration. Simple product of QRS voltage and duration, as an approximation of the time–voltage integral of the QRS complex,20 significantly improve electrocardiographic LVH identification compared with voltage criteria alone. Nonetheless, voltage product indexes still exhibit relatively poor sensitivities for LVH detection at the high levels of specificity necessary for satisfactory clinical utility.

Various previous studies6–9,21–23 demonstrated associations between QT interval parameters and echocardiographic LVM in selected and unselected groups of hypertensive patients. Nevertheless, only a few8,9,23 evaluated whether these relationships were strong enough for QT interval measurements to be recommended as an isolated screening method for LVH detection. Only one of these studies23 reported a better performance of 1 QT parameter (QTcmax duration in lead I) than simpler ECG voltage indexes for LVH detection, but this study involved only 47 patients, a relatively small number of highly selected hypertensives, which probably explains this discrepancy. The other 2 studies8,9 support our findings that when used in isolation, all QT interval–derived parameters showed a high specificity but a low sensitivity at most equivalent to ECG voltage criteria.

Two features of this study are original. It is, as far as we know, the first study to assess QT interval parameters in patients with RH, a particular understudied subgroup of hypertensive patients with an expected high cardiovascular morbidity and mortality.24 Furthermore, we also demonstrate that the combination of both variables, QT interval measures and ECG voltage indexes, improves LVH risk stratification compared with either alone.

Prolonged QT interval parameters are presumed to represent measures of abnormal ventricular repolarization,25 a condition demonstrated experimentally to exist in the hyper-
trophyed myocardium with interstitial fibrosis.26,27 These altered electrophysiological properties induced by LVH are potentially arrhythmogenic28,29 and may be the functional substrate for the increased incidence of sudden death in hypertensives with LVH. Also, experimentally, regression of LVH normalizes LVH-induced proarrhythmic repolarization abnormalities,28,30 whereas reduction in LVM and regression of electrocardiographic LVH indexes are associated with QT interval shortening.31 Finally, it was demonstrated recently that QT parameters are predictors of cardiovascular mortality in hypertensive patients with electrocardiographic LVH10 and with type 2 diabetes,11 as it was already known for electrocardiographic indexes of LVH.32,33 Therefore, it appears reasonable to speculate that QT interval parameters and ECG voltage indexes could act in combination not only to determine an increased chance of having electrocardiographic LVH, but also to identify a subgroup of hypertensive patients with a high cardiovascular risk profile, particularly for sudden arrhythmic death. This hypothesis clearly needs confirmation from properly designed prospective studies.

In this group of RH patients evaluated, the best QT parameters associated with LVH were derived from QT end interval measurements. QT peak interval, which excludes the terminal portion of T wave, where most of regional ventricular repolarization disparities are presumed to lie,34 and JT interval measures, which excludes ventricular activation that can be delayed in LVH, showed weaker associations with LVH than the entire QT end interval parameters. Therefore, probably by reflecting ventricular depolarization and repolarization abnormalities, QT end-derived parameters have advantages over other components of the QT interval. Also, between the 2 best QT parameters, we prefer QTc max interval duration because of its significantly better measurement reproducibility and standardization than QTd. Furthermore, QTc max interval duration has also established biological significance, whereas that of QTd is still controversial.25

Some limitations of this study are important to note. First it has a cross-sectional design, so we deal with prevalences and no inference about LVH incidence or change over time can be made. So considerations about the value of QT parameters for prediction of echocardiographic LVH occurrence are speculative and should be faced with caution. The association of QT parameters and echocardiographic LVH may reflect different and complementary aspects of the same physiopathological process. Moreover, some associations observed may have been influenced by the survival effect. For example, patients with LVH had significantly lower serum total cholesterol than those without LVH. Second, because this study included only patients with RH, a group with a high prevalence of LVH, it affects the generalizability of the present results to other less severe hypertensive patients. Thus, the value of combining QT interval parameters and ECG voltage criteria for LVH detection should also be tested in other unselected hypertensive populations.

### Perspectives

This study provides evidence that although in isolation, no QT interval–derived parameter is better than simple ECG voltage criteria, in combination, they improve echocardiographic LVH detection, compared with either alone, in resistant hypertensive patients with a high prevalence of LVH. It needs to be studied prospectively whether these variables are also capable of identifying a subgroup of patients with a high risk of cardiovascular morbidity and mortality, particularly in relation to sudden death incidence. Furthermore, intervention studies are necessary to evaluate whether LVH regression is accompanied by normalization of QT interval prolongation and its impact on arrhythmogenesis.

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### References


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