Is QT Dispersion Associated with Sudden Cardiac Death in Patients with Hypertrophic Cardiomyopathy?

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QT dispersion is significantly greater in patients with hypertrophic cardiomyopathy (HCM) than that in healthy subjects. Few data exist regarding the prognostic value of QT dispersion in HCM. In this study, we retrospectively investigated the association between QT dispersion and sudden cardiac death in 46 patients with HCM (mean 33.1 ± 15.5 years, 32 men). The case group consisted of 23 HCM patients who died suddenly, and the control group consisted of 23 HCM patients who survived uneventfully during follow-up. Study patients were pair-matched for age, gender, and maximum left ventricular wall thickness. QT dispersion (maximum minus minimum QT interval) was manually measured on early 12-lead ECGs using a digitizing board. An in-house program was used for calculating QT interval, QT dispersion, JT interval, and JT dispersion (maximum minus minimum J point to T end interval). Patients in the case group tended to have shorter RR intervals than those in the control group (777 ± 171 vs 856 ± 192 ms, $P = 0.08$). Maximum corrected QT and JT intervals did not discriminate the case group from controls (489 ± 29 vs 479 ± 27 ms, $P = \text{NS}$; 375 ± 36 vs 366 ± 22 ms, $P = \text{NS}$, respectively). Greater QT dispersion and JT dispersion were found in the case group compared with controls (74 ± 28 vs 59 ± 21 ms, $P = 0.02$ and 76 ± 32 vs 59 ± 26 ms, $P = 0.03$, respectively). The measurements of maximum QT, JT, and T peak to T end intervals, precordial QT and JT dispersion, and T peak and T end dispersion were all comparable between the two groups ($P = \text{NS}$ for all). No systematic changes in ECG measurements were found from late ECGs of the case group compared to those from early ECGs ($P = \text{NS}$). No correlation between maximum left ventricular wall thickness and QT dispersion, JT dispersion, maximum QTc or JTc intervals was observed ($r < 0.29$, $P > 0.05$ for all). Our results show that increased QT dispersion and JT dispersion is weakly associated with sudden cardiac death in the selected patients with HCM.

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QT dispersion; sudden death; hypertrophic cardiomyopathy; electrocardiogram

INTRODUCTION

Sudden death is a feature of hypertrophic cardiomyopathy (HCM) in its natural history and occurs often in patients who had no or mild symptoms.¹ Identification of patients who are at high risk of sudden death remains a

major challenge in clinical management. Although numerous studies have been conducted to find the risk markers for sudden death in past decades, no single marker has been demonstrated to be sensitive or specific enough to meet clinical need. A combination of different risk factors may improve the predictive accu-

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racy for sudden death.² Noninvasive electrocardiographic markers for sudden death are desirable for clinical risk stratification.

QT dispersion was thought to reflect the heterogeneity of ventricular repolarization.³ A number of studies have demonstrated that QT dispersion is associated with malignant ventricular tachyarrhythmias, sudden death, or cardiovascular mortality in a variety of patient populations.⁴⁻⁷ Few data exist regarding the clinical importance of QT dispersion for identifying patients at high risk of sudden death in HCM. This study evaluates the association between QT dispersion and sudden death in well-defined patients with HCM.

METHODS

Study Patients

The study population consisted of 46 patients (mean age 33.1 ± 15.5 years, range 11-65 years; 32 men) with confirmed diagnosis of HCM who were diagnosed and followed up (53 ± 34 months) in St George's Hospital up to 1998. HCM was defined by the presence of left ventricular hypertrophy on two-dimensional echocardiography in the absence of other cardiac or systemic diseases that cause left ventricular hypertrophy.⁸ All patients fulfilled the conventional diagnostic criteria for HCM. Twenty-three patients who suffered from sudden cardiac death during follow-up were compared with an equal number of HCM patients who survived uneventfully by the time of their last follow-up. An attempt was made to pair-match study patients for age (targeted within 5 years), gender, and maximum left ventricular wall thickness (targeted within 3 mm). Patients with atrial fibrillation, atrioventricular block, or sinus node dysfunction were excluded from this study. In addition, patients who had ECG recordings with very flat T waves or excessive noise were also excluded.

Electrocardiographic Recordings and Measurements

The initial standard 12-lead ECGs, which were recorded at the patient's first visit to St. George's Hospital, were analyzed in this study. The last available subsequent ECGs were also studied, provided it met the ECG measurement criteria.

All study ECGs were recorded at a paper speed

of 25 mm/s. QT intervals were measured from the onset of the QRS complex to the end of the T wave, defined as a return to the TP baseline (baseline between the end of the T wave and the following P wave) or the nadir of the curve between the T wave and U waves, when the latter were present. Two consecutive QRS complexes were measured from each lead, whenever possible, and the averaged value were finally used for data analysis. Where the end of the T wave could not be identified with certainty, that lead was excluded from the analysis. ECG leads of poor quality were also excluded from the measurement. At least six measurable ECG leads were required for this study. No attempt was made to correct for missing leads.⁹ All measurements were performed by a single experienced observer blinded to clinical status.

QT intervals were measured manually using a high resolution (0.1 mm to 4 ms) digitizing board (Cherry, Harpender, United Kingdom) driven by a purpose-built interactive software. An in-house program was used for calculating QT interval, as well as QT dispersion. To eliminate the confounding factor of bundle branch block from QT analysis, JT interval and JT dispersion were also calculated on the same data set. QT dispersion was defined as the difference between longest and shortest QT intervals across any of the 12 leads (global QT dispersion) or across any of the 6 precordial leads (precordial QT dispersion). The same principle applied to the JT dispersion. In addition, global T-peak and T-end interval duration and dispersion were derived from the same data.

Data Analysis and Statistics

In this study, maximum interval durations, which were denoted as the maximum interval in any lead of the measured leads, were used in the final analysis. Bazett's formula was used to correct QT interval (QTc) and JT interval (JTc) for heart rate, but only uncorrected values were used for the assessment of ventricular repolarization dispersion in this study.¹⁰ Only global T peak to T end dispersion was analyzed.

To compare the numeric values of all measurements between study groups, a Student's two-tail paired or unpaired *t*-test was used, where appropriate. Pearson's product moment correlation was used for assessing the relation between electrocar-

diographic measurements and echocardiographic features.

Continuous variables were presented as mean $\pm$ 1 standard deviation. A P value of < 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

The clinical characteristics of study patients are listed in Table 1. All patients were well pair-matched within the target ranges except for three pairs. In one pair of patients, there was 7 years difference in age but both case and control patients were < 25 years old. In another two pairs, the differences in maximum left ventricular wall thickness were between 5 to 7 mm and all four patients had a measurement of maximum left ventricular wall thickness > 20 mm. Maximum QRS complex duration > 120 ms was present in 8 (17%) of study patients. There were no significant differences in any clinical variables between the two study groups ($P = \text{NS}$ for all).

Electrocardiographic Measurements on Early ECGs

At least 8 leads (mean 11.0 ± 1.5) were measured from each ECG. Electrocardiographic measurements from all study patients and from each group are presented in Table 2.

In patients with sudden cardiac death, both global QT and JT dispersion were significantly greater than those in the control group (74 ± 28 vs 59 ± 21 ms, $P = 0.02$; 76 ± 32 vs 59 ± 26 ms, $P = 0.03$, respectively). Individual measurements of global QT and JT dispersion are illustrated in Figure 1. All other measurements were comparable between study groups ($P = \text{NS}$).

Comparison of the Electrocardiographic Measurements of Ventricular Repolarization between Early and Late ECG Recordings

Fifteen late ECGs from patients who died suddenly were available and measurable for this study. No systemic changes in the measurements from late ECG recordings were observed compared with those from early ones. None of the differences in the measurements between early and late recordings reached statistical significance, but only 15 of 23 patients were studied, so this result has to be interpreted cautiously.

Relation between Measurements of Ventricular Repolarization Duration or Dispersion and Clinical Variables

No correlation was found between maximal left ventricular wall thickness and neither global QT/JT dispersion nor precordial QT/JT dispersion. The

Table 1. Clinical Characteristics of Study Patients with Hypertrophic Cardiomyopathy

	Patients With SCD (n = 23)	Patients Without SCD (n = 23)
Age (years)	32.5 ± 15.9	33.8 ± 15.4
Gender (men)	16 (70%)	16 (70%)
Syncope	8 (35%)	4 (17%)
Family history of HCM and SCD	7 (30%)	4 (17%)
Exertional chest pain	10 (43%)	11 (48%)
Dyspnea (class $\geq$ II)	10 (43%)	8 (35%)
Abnormal BP	7 (30%)	5 (22%)
Nonsustained VT on Holter monitoring	5 (22%)	7 (30%)
Maximal LVWT (mm)	25.5 ± 6.3	25.6 ± 6.6
LVEDD (mm)	41.4 ± 5.6	41.1 ± 6.7
LVESD (mm)	23.5 ± 6.4	22.5 ± 5.8
Left atrial diameter (mm)	40.4 ± 9.6	41.9 ± 6.2
Left ventricular gradient > 30 mmHg	1 (4%)	2 (9%)
QRS widening (> 120 ms)	3 (13%)	5 (22%)
Antiarrhythmic or β blockage therapy	4 (17%)	3 (13%)

BP = blood pressure response during upright exercise; HCM = hypertrophic cardiomyopathy; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVWT = left ventricular wall thickness; SCD = sudden cardiac death; VT = ventricular tachycardia.

Table 2. Electrocardiographic Measurements (Mean $\pm$ SD) in Hypertrophic Cardiomyopathy Patients With and Without Sudden Cardiac Death During Follow-up

ECG Parameters	All Patients (n = 46)	Patients With SCD (n = 23)	Patients Without SCD (n = 23)	P Values*
Mean RR (ms)	816 $\pm$ 184	777 $\pm$ 171	856 $\pm$ 192	0.08
Mean QRS (ms)	101 $\pm$ 15	99 $\pm$ 14	102 $\pm$ 15	0.25
Max QT (ms)	434 $\pm$ 50	429 $\pm$ 57	439 $\pm$ 42	0.23
Max QTc (ms)	484 $\pm$ 29	489 $\pm$ 29	479 $\pm$ 27	0.13
g-QTd (ms)	66 $\pm$ 26	74 $\pm$ 28	59 $\pm$ 21	0.02
p-QTd (ms)	51 $\pm$ 23	55 $\pm$ 23	46 $\pm$ 23	0.11
Max JT (ms)	333 $\pm$ 47	329 $\pm$ 54	337 $\pm$ 40	0.30
Max JTc (ms)	370 $\pm$ 30	375 $\pm$ 36	366 $\pm$ 22	0.18
g-JTd (ms)	67 $\pm$ 30	76 $\pm$ 32	59 $\pm$ 26	0.029
p-JTd (ms)	49 $\pm$ 23	52 $\pm$ 22	46 $\pm$ 24	0.18
Max TpTe (ms)	113 $\pm$ 17	110 $\pm$ 16	116 $\pm$ 18	0.13
TpTeD (ms)	41 $\pm$ 14	38 $\pm$ 13	43 $\pm$ 15	0.12

* P values for comparison between patients with and without sudden cardiac death; g-JTd = global JT dispersion; g-QTd = global QT dispersion; JT = JT interval; JTc = heart rate corrected JT interval; Max = maximum; p-JTd = precordial JT dispersion; p-QTd = precordial QT dispersion; QRS = QRS complex duration; QT = QT interval; QTc = heart rate corrected QT interval; RR = RR interval; SCD = sudden cardiac death; TpTe = T peak to T end interval; TpTeD = T peak to T end dispersion.

measurements of maximal left ventricular wall thickness was not correlated with maximum QT/JT interval or heart rate corrected QT or JT intervals ($r < 0.29$, $P > 0.05$ for all).

There were no differences in QT, JT or T peak, and T end dispersion between patients with and without a family history of sudden cardiac death and HCM, with and without an abnormal blood

Figure 1. Individual measurements of global QT dispersion (1A) and global JT dispersion (1B) in hypertrophic cardiomyopathy patients with (large dots) and without sudden cardiac death (small dots).

pressure response during exercise testing, with and without recurrent syncope or nonsustained ventricular tachycardia on Holter monitoring in the study population ($P > 0.05$ for all).

DISCUSSION

In this study, we measured the QT intervals from surface ECG and found an apparent trend towards an increased QT (and JT) dispersion in HCM patients with sudden cardiac death compared with pair-matched event-free survivors with HCM. The measurements of ventricular repolarization dispersion were not correlated with echocardiographic features, or the recognized risk factors.²

QT Dispersion and Sudden Cardiac Death in HCM

Previous studies^{4,11-13} have clearly shown that QT dispersion is significantly greater in patients with HCM than that in normal subjects. However, the importance and clinical relevance of an increased QT dispersion has not been fully explored in patients with HCM. An early study showed that increased QT dispersion distinguished patients with ventricular tachyarrhythmias from those without the arrhythmias in a small HCM population ($n = 26$).⁴ The association between QT dispersion measurements and the recognized risk factors for sudden death was examined using prospectively collected ECG data in a relatively larger population ($n = 83$) but that study did not demonstrate any significant association between them.¹¹ In that study, however, no endpoints (such as sudden death or cardiac death) were available for further prognostic assessment. In a recent study,¹³ 254 initial ECGs of HCM patients were retrospectively analyzed. No significant differences in QT dispersion were found between survivors and those with either sudden death or disease-related death. But their study patients were not matched for the severity of myocardial hypertrophy, which has been shown to be directly related to the risk of sudden cardiac death in HCM.^{2,14} Preliminary genotype-phenotype correlation studies have shown that gene mutations carry prognostic significance, and cardiac troponin T (cTnT) gene mutation carriers are more likely to have a poor prognosis.¹⁵⁻¹⁷ A recent study showed that QT dispersion failed to differentiate between a group with a cTnT mutation and those with a β -myosin heavy chain gene

mutation, which is associated with a good prognosis.¹⁸ This finding did not support the idea that QT dispersion was associated with sudden cardiac death in HCM. Although the present study demonstrates a tendency of a significantly increased QT dispersion and JT dispersion in HCM patients who suffered from sudden cardiac death, the measurements are largely overlapped between cases and controls.

Although a number of studies showed that QT dispersion appeared to be a useful predictor of adverse cardiac events in a variety of patient populations,³⁻⁷ conflicting results exist.^{19,20} The lack of a strong association between QT dispersion and sudden death in this study may be explained in several ways. The QT dispersion was measured on patients' early ECGs and sudden death may occur at months or years after the studied ECGs were taken. Ventricular repolarization is a dynamic process and it is unlikely that any arrhythmic substrate would remain stable over a very prolonged period. Thus, a single measurement from an early recording may be unable to predict late events. On the other hand, our measurements from late ECGs of a small number of patients did not appear encouraging. Second, QT dispersion might be a sensitive, but not specific marker of sudden cardiac death from a surface ECG. Last, QT dispersion may not represent the heterogeneity of ventricular repolarization as it was thought.²¹ The notion that QT dispersion from 12-lead ECG reflects the heterogeneity of ventricular repolarization has been opened to question.^{21,22}

Study Limitation and Implication

Assessment of QT dispersion from surface ECGs is well known to have a number of limitations.^{23,24} Despite the knowledge that reliability of QT measurement is influenced by the amplitude of T waves, noise, paper speed of recording, instruments for the measurements, type of algorithm and other factors, we performed a manual QT measurement on paper recordings simply because of the limitation of such a retrospective study. To minimize the measurement inaccuracy, a high resolution digitizing board (0.1 mm to 4 ms) was used in conjunction with an in-house program in the present study. This study was designed as a case-control study on strictly pair-matched patients in relation to age, gender,²⁵ and the severity of myocardial hypertrophy^{2,11,14} to eliminate the common

confounding factors. Though our measurements may reflect the underlying differences in ventricular repolarization between study groups, this study was performed on a small, selected population; the findings may not be extrapolated to a larger unselected population of HCM.

Electrocardiographic QT measurement is subject to measuring errors, but QT dispersion is not simply a result of measurement error.²⁶ Intrinsic variation in QT intervals across 12 leads may outweigh inaccuracies introduced by other factors, including measurement errors and interobserver variability.²⁷ QT dispersion could be a crude measure of abnormalities during the whole course of repolarization. A significantly increased QT dispersion (e.g., ≥ 100 ms) may be interpreted as a marker of an abnormal course of the ventricular repolarization,²⁶ but clinical intervention cannot be made simply based on QT dispersion assessment alone. The possibility that a significantly increased QT dispersion, combined with other risk indicators, might have implications for risk assessment cannot be firmly excluded without prospective studies in large well-defined populations. Even though the value of the present study is limited by its retrospective nature and relatively small population, these results do not favor the idea that a simple measurement of QT dispersion alone may be used as a clinical tool for prospective identification of individual patients with HCM who are at risk of sudden death.

Further Electrocardiographic Assessment of Ventricular Repolarization

Substantial variability in QT dispersion measurements has limited its practical value in risk stratification.^{28,29} A new concept of assessment of T wave morphology has emerged. In contrast to the conventional QT-based method for assessment of ventricular repolarization, the major advantage of recently developed techniques for T wave morphology assessment is its independence of the location of T end.³⁰ Promising results have been reported recently, which provided important information for risk stratification in patients after myocardial infarction.^{31,32} In patients with HCM, T wave abnormalities are common. A comprehensive evaluation of T wave morphology will probably be of greater clinical value by providing additional information associated with ventricular repolarization abnormalities and sudden cardiac death.

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