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T-Peak to T-End Interval May Be a Better Predictor of High-Risk Patients with Hypertrophic Cardiomyopathy Associated with a Cardiac Troponin I Mutation Than QT Dispersion

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Summary

Background: Patients with hypertrophic cardiomyopathy (HCM) associated with a deletion of lysine 183 (K183del) in the cardiac troponin I (cTnI) gene suffer sudden cardiac death at all ages. However, the correlation between QT variables and sudden cardiac death in these patients remains uncertain.

Hypothesis: We evaluated the correlation between QT variables and sudden cardiac death and/or ventricular tachyarrhythmia (SCD/VT) in patients with HCM associated with the cTnI mutation.

Methods: We analyzed 10 probands with HCM associated with the cTnI gene K183del and their family members. The subjects were divided into three groups: Group A (n = 7), mutation carriers with SCD/VT; Group B (n = 16), mutation carriers without SCD/VT; Group C (n = 24), no mutation carriers. QT intervals were corrected using Bazett's formula.

Results: Maximum QTc and corrected QT dispersion were significantly longer in Groups A and B than in Group C. However, there were no differences in either parameter between Groups A and B. On the contrary, the peak-to-end interval of T wave/QT interval in V_5 (Tpe) in Group A was significantly longer than that in Groups B and C. Logistic regression analysis revealed that Tpe was a good clinical predictor for SCD/VT in patients with HCM in this study.

Conclusions: These results suggest that Tpe rather than QT dispersion may be one of the best predictors for SCD/VT in patients with HCM associated with the K183del mutation in the cTnI gene.

Key words: hypertrophic cardiomyopathy, troponin I, QT dispersion, transmural QT dispersion

Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease with respect to morphology, pathophysiology, and genetics. Recent advances in molecular genetics revealed that HCM is caused by mutations in the genes encoding sarcomeric proteins, such as β-myosin heavy chain, cardiac troponin T, and cardiac troponin I (cTnI).[1] Analyses of genotype-phenotype correlation revealed that phenotypic heterogeneity may be due in part to genetic heterogeneity.[1] On the other hand, patients with HCM are at high risk for sudden cardiac death and/or malignant ventricular tachyarrhythmia (SCD/VT).[2] Moreover, sudden cardiac death may be the first clinical manifestation.[3] Therefore, it is necessary to determine a predictor of SCD/VT for each genotype.

QT variability between leads on the surface electrocardiogram (ECG), defined as QT dispersion (QTD), is a proposed marker for SCD/VT in patients with HCM.[4, 5] In contrast, another report found no significant association between QTD and any risk factors for sudden cardiac death in patients with HCM.[6] The association between QTD and SCD/VT in patients with HCM remains controversial. On the other hand, a recent study reports that transmural QTD is associated with

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ventricular tachyarrhythmia, and that the peak-to-end interval of the T wave serves as an index of transmural dispersion of repolarization.[7] It is unclear what parameter on the surface ECG is associated with transmural dispersion of wedge preparation model. We hypothesize that the peak-to-end interval of the T wave in left precordial leads on the surface ECG may be a good predictor of SCD/VT if it reflects the transmural dispersion of left ventricle (LV).

We reported that patients of all ages with HCM associated with a deletion of lysine 183 (K183del) in the cTnI gene had sudden death;[8] however, a predictor of SCD/VT in these patients remains unclear. Therefore, this study was performed to evaluate QT variables in these patients and to investigate the correlation between these QT variables and SCD/VT.

Methods

Subjects

Ten unrelated probands with HCM associated with K183del in the cTnI gene, identified by genetic analysis at the Kanazawa University, were studied. Informed consent was obtained from all subjects. After detection of the K183del mutation in the cTnI gene (see below), ECG, echocardiogram, and peripheral blood samples were obtained for analysis of this mutation from as many other family members as possible. Moreover, subjects with the mutation were evaluated for ventricular tachycardia by 24-h Holter monitoring. Among the 10 pedigrees studied, 10 patients experienced sudden cardiac death. Three of the 10 patients had ECGs recorded within 1 month of sudden death. Therefore, these three patients were included in this study as carriers of the mutation. Subjects were excluded from this study according to the following guidelines: young subjects < 18 years old; patients who had atrial fibrillation; patients with conduction disturbances; mutation carriers without Holter monitoring; and subjects with inadequate ECG for evaluation of QT variables. Subjects were divided into three Groups: Group A included mutation carriers with SCD or VT on Holter monitoring; Group B included mutation carriers without SCD and VT on Holter monitoring; and Group C consisted of subjects who were not carriers of the mutation.

Detection of Mutation

DNA was isolated from peripheral white blood cells from all subjects using a DNA Extractor 341 Nucleic Acid Purification System (Genepure™, PE Biosystems, Foster City, Calif., USA) In vitro amplification of genomic DNA was performed via polymerase chain reaction (PCR). Oligonucleotide primers were used to amplify exon 7 of the cTnI gene as described previously.[9] Single-strand conformational polymorphism (SSCP) analysis of amplified DNA was then performed using a previously described method,[10] with a slight modification. For abnormal SSCP patterns, PCR products were subcloned into the pCR2.1 vector by using the TOPO TA cloning kit (Invitrogen, Carlsbad, Calif., USA) The nucleotide sequence of the cloned PCR products was determined on both strands by the dye terminator cycle sequencing method using an automated fluorescent sequencer (ABI Prism™ 310 Genetic Analyzer, PE Biosystems). Family members of the affected probands were evaluated similarly.

QT Interval Measurements

All 12-lead ECGs were recorded at 25 mm/s with standard lead positions. All records were clearly magnified by 200%, and QT intervals were measured. Electrocardiogram analyses of the patients with SCD were performed using the last ECGs recorded before death. To eliminate both interobserver variability and bias, QT intervals were measured using a digitizer in each of the 12 leads by a single observer who was blinded to all clinical findings. QT intervals were taken to be from the onset of the QRS complex to the end of the T wave. The end of the T wave was defined as an intersecting point of a tangent line on the terminal T wave and the T-P baseline. QT intervals were corrected for heart rate using Bazett's formula: $QTc = QT/(RR)^{1/2}$. QTD was calculated as the difference between the maximum QT (maxQT) and minimum QT (minQT) intervals measured on all 12 leads of the ECG, and corrected QTD (QTDc) was calculated as the difference between maxQTc and minQTc. If the height or depth of the T wave was < 1.5 mm, its lead was excluded from analysis. A limit of six or more leads per ECG was arbitrary and chosen to exclude ECGs of inadequate technical quality from analysis.[11] Moreover, the peak-to-end interval of the T wave divided QT interval in V_5 lead was measured as new index (Tpe). This measurement was performed using more than three consecutive QRST records, and the average value was calculated. Intraobserver variability in the measurements of QTD and Tpe were calculated by using 35 randomly selected and duplicated ECGs from all subjects.

Echocardiographic Examinations

Standard transthoracic M-mode and two-dimensional echocardiographic studies were performed to identify and quantify morphologic features of the left ventricle. Left ventricular (LV) dimensions and the thicknesses of the septum and posterior LV wall were measured at the level of the tips of the mitral valve leaflets. The fractional shortening was calculated as the difference in end-diastolic and end-systolic dimensions divided by the end-diastolic dimension.

Statistical Analysis

Values are expressed as the mean ± standard deviation (SD). Differences between two groups were analyzed by Student's unpaired *t*-test. Comparison among the three groups was performed using a one-way analysis of variance (ANOVA) followed by Scheffe's method. Categorical data were compared using chi-square analysis. Logistic regression analysis was performed using StatView 5.0 (Abacus Concepts, Inc., Berkeley, Calif., USA). A p value of < 0.05 was considered statistically significant.

Results

Clinical and Echocardiographic Data

Group A consisted of 7 patients (3 with SCD, 1 with a history of sustained VT, and 3 with nonsustained VT on Holter monitoring), Group B consisted of 16 patients, and Group C consisted of 24 subjects. The clinical characteristics and echocardiographic data of the study subjects were summarized in Table I. No patient had LV outflow tract gradient > 30 mmHg. No patient received amiodarone or sotalol therapy.

Electrocardiographic Analysis

The results of QT analysis are summarized in Table II. The average absolute values of intraobserver variability of QTDc and Tpe were 2 ms and 0.006, respectively. The maxQTc in Groups A and B were significantly larger than those in Group C, but there was no difference between maxQTc in Groups A and B. The minQTc did not differ among three groups. Corrected QTD was significantly larger in Groups A and B than in Group C. However, QTDc did not differ between Groups A and B, as shown in Figure 1. On the contrary, Tpe in Group A was significantly larger than in Groups B and C, as shown in Figure 2.

Logistic regression analysis revealed that in QT variables QTDc was not a good predictor, while Tpe was the best predictor for SCD/VT in these patients. Analysis of the relative cumulative frequency of Tpe revealed that Tpe of 0.196 was the cutoff value with the greatest accuracy for detecting SCD/VT in patients with HCM. The sensitivity, specificity, and positive and negative predictive values of Tpe > 0.200 for predicting SCD/VT were 71, 75, 56, and 86%, respectively.

Discussion

In the present study, we found that patients with HCM associated with a K183del mutation in the cTnI gene had large QTDc and Tpe, and that Tpe in patients with SCD/VT was larger than that in patients without SCD/VT.

QT Dispersion and Ventricular Tachyarrhythmia

Significantly prolonged maxQT and QTD values were reported in patients with HCM.[3, 10] QTD is thought to reflect regional heterogeneity of the ventricular repolarization, and prolonged QTD correlates with the incidence of ventricular tachyarrhythmias and sudden death in patients with HCM.[4, 5] On the contrary, Yi *et al.*[6] reported that no significant association was found between QTD and any risk factors for sudden death in patients with HCM. The relation between QTD and sudden death in patients with HCM remains uncertain.

Recent studies have shown that HCM is caused by mutations in genes that encode sarcomeric proteins. Moreover, studies regarding genotype-phenotype correlation revealed that prognosis of HCM varies according to genotype. For example, the Arg403Gln β-myosin heavy chain (βMHC) gene mutation is associated with a high incidence of sudden death, while the Val908Met mutation is associated with a benign prognosis.[12] Some mutations in the cardiac troponin T gene are associated with a high incidence of sudden cardiac death,[13, 14] while mutations in the gene for myosin-binding protein C are associ-

TABLE I Baseline characteristics

	Group A (mutation carrier with SCD/VT)	Group B (mutation carrier without SCD/VT)	Group C (no mutation)
Number of cases	7	16	24
Male (%)	4 (57)	7 (44)	13 (54)
Age	50.6 ± 14.6	43.8 ± 16.6	44.1 ± 17.9
History of chest pain (%)	5 (71) [a]	4 (25)	—
History of syncope (%)	2 (29)	1 (6)	—
Echocardiogram			
IVST (mm)	19.4 ± 3.4 [d]	17.8 ± 4.7 [d]	9.6 ± 1.4
PWT (mm)	12.1 ± 3.1 [c]	10.8 ± 1.6 [b]	9.1 ± 1.2
IVST/PWT	1.66 ± 0.40 [d]	1.66 ± 0.40 [d]	1.05 ± 0.11
LAD (mm)	45.9 ± 8.2 [d]	39.3 ± 7.2 [b]	33.0 ± 5.1
EDD (mm)	46.6 ± 2.5	46.1 ± 5.7	48.4 ± 3.4
ESD (mm)	32.9 ± 5.3	28.3 ± 5.1	30.8 ± 3.7
FS (%)	29.7 ± 8.2 [b]	38.8 ± 8.3	36.3 ± 6.5
Medication			
Beta blocker (%)	1 (14)	2 (13)	—
Ca antagonist (%)	1 (14)	5 (31)	—
Amiodarone or sotalol	0	0	—

Values are mean ± standard deviation unless stated.

[a] $p < 0.05$ vs. Group B, [b] $p < 0.05$ vs. Group C, [c] $p < 0.01$ vs. Group C, [d] $p < 0.001$ vs. Group C.

Abbreviations: SCD/VT = sudden cardiac death and/or ventricular tachyarrhythmia, IVST = interventricular septal thickness, PWT = left ventricular posterior wall thickness, LAD = left atrial dimension, EDD = left ventricular end-diastolic dimension, ESD = left ventricular end-systolic dimension, FS = fractional shortening, Ca = calcium.

TABLE II Electrocardiographic data

	Group A (mutation carrier with SCD/VT)	Group B (mutation carrier without SCD/VT)	Group C (no mutation)
RR (ms)	925 ± 216	934 ± 145	898 ± 128
maxQT (ms)	430 ± 61 [b]	426 ± 50 [c]	380 ± 29
minQT (ms)	377 ± 56	372 ± 47	345 ± 28
QTD (ms)	53 ± 19 [b]	54 ± 19 [d]	34 ± 11
maxQTc	450 ± 42 [c]	442 ± 37 [c]	401 ± 25
minQTc	394 ± 28	386 ± 37	364 ± 21
QTDc	56 ± 22 [b]	56 ± 20 [c]	37 ± 12
Tpe	0.233 ± 0.047 [a,c]	0.173 ± 0.034	0.185 ± 0.018

Values are mean ± standard deviation.

[a] $p < 0.001$ vs. Group B, [b] $p < 0.05$ vs. Group C, [c] $p < 0.01$ vs. Group C, [d] $p < 0.001$ vs. Group C.

Abbreviations: SCD/VT = sudden cardiac death and/or ventricular tachyarrhythmia, maxQT = maximum QT interval, minQT = minimum QT interval, QTD = QT dispersion, maxQTc = corrected maximum QT interval, minQTc = corrected minimum QT interval, QTDc = corrected QT dispersion, Tpe = peak-to-end interval of T wave divided QT interval in V_5.

ated with a relatively favorable prognosis.[15, 16] These reports suggest that different genotypes are associated with different ECG findings, especially regarding QTD. Accordingly, it is necessary to investigate the correlation between QTD and sudden death in each genotype. This is the first report regarding the correlation between QTD and SCD/VT in patients with HCM associated with a K183del mutation in the cTnI gene. In this study, QTD did not differ between Groups A and B. This result suggests that QTD may not be useful as a predictor of SCD/VT in patients with the K183del mutation in cTnI gene. Regarding other gene mutations, it has been reported that QTD did not correlate with arrhythmia inducibility in mice with HCM resulting from a mutation in the β-myosin heavy chain gene (Arg403Gln).[17] Regional variability in the repolarization may not play an important role for occurrence of malignant ventricular tachyarrhythmia in patients with these mutations. Using another method, Atiga *et al.*[18] reported that QT variability index was higher in patients with HCM than in controls, and that it was greatest in patients with the Arg403Gln mutation. Further investigation will be necessary to establish the correlation between QTD and arrhythmic events in patients with other gene mutations.

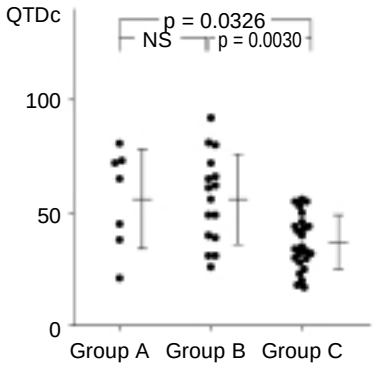

FIG. 1 Comparison of corrected QT dispersion (QTDc) among the three groups. NS = not significant.

Peak-to-End Interval of T Wave and Ventricular Tachyarrhythmia

This study revealed that Tpe in patients with SCD/VT was significantly longer than that in patients without SCD/VT. Antzelevitch *et al.*[7, 19] recently reported the interesting finding that transmural QTD is associated with ventricular tachyarrhythmias and transmural QTD is reflected in the peak-to-end interval of the T wave. It is unclear how much Tpe in a human model may reflect the transmural QTD in an experimental model, and that transmural QTD is associated with ventricular tachyarrhythmias in humans. However, we hypothesized that the peak-to-end interval of the T wave may be a useful predictor of SCD/VT if $V_{1–6}$ leads reflect an electrical phenomenon in each region and the peak-to-end interval of the T wave reflects transmural QTD of the left ventricle near the electrode. After consideration of the effect of heart rate variability, we used the index of the peak-to-end interval of the T wave divided by the QT interval in the same lead. This study

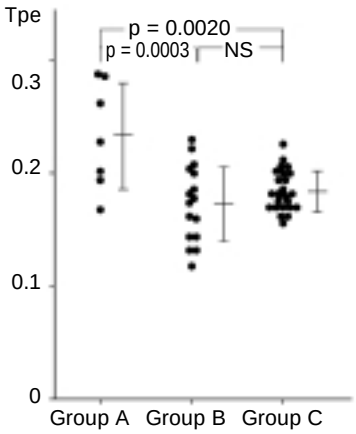

FIG. 2 Comparison of peak-to-end interval of T wave, divided by the QT interval in V_5 lead, (Tpe) among the three groups. NS = not significant.

demonstrated that Tpe correlates with SCD/VT in patients with HCM associated with a K183del mutation in the cTnI gene, and that it may be useful as a predictor of SCD/VT in these patients. These results also suggest the possibility that ventricular tachyarrhythmia in patients with HCM associated with the K183del mutation in cTnI gene may be associated with transmural QTD rather than regional QTD; however, an overlap is found in Tpe in patients with and without SCD/VT. Possible reasons may include not only transmural dispersion but also other causes that take part in SCD/VT. In addition, one Holter monitoring cannot catch all ventricular tachycardia. Although these points are unclear, this study suggests that patients with HCM and Tpe > 0.200 were followed closely. Further investigation of the correlation between Tpe and transmural QT dispersion will be required. Moreover, the usefulness of the index, Tpe, for a predictor of SCD/VT in patients with HCM associated with other mutation should be also studied.

Study Limitations

In this study, we measured the QT interval and T-wave peak-to-end interval manually since we did not have an automated measurement system for these variables. However, the manual measurement did not have a significant effect on our results as shown by the small intraobserver variability.

Our study excluded patients under 18 years old for the following reasons: (1) there were few young patients with the mutation who also had Holter monitoring, and (2) differences in wall thickness and heart size between young patients and adult patients may affect QT variables. However, SCD was found not only in adult patients but also in young patients with this mutation.[8] Therefore, the usefulness of Tpe as a predictor for SCD/VT should be evaluated in young patients with K183 del mutation in cTnI gene in the future.

In this study, the numbers of patients in all three groups were small because they were necessarily restricted to those with K183del mutations in the cTnI gene. Moreover, the confidence intervals are wide. Additional studies including larger samples are necessary to confirm and clarify our results.

Conclusions

In family members of patients with HCM associated with the cTnI mutation, QTD did not differ between mutation carriers with and without SCD/VT. On the contrary, Tpe in mutation carriers with SCD/VT was significantly longer than in those without SCD/VT. The Tpe may be a better clinical predictor for SCD/VT in patients with HCM associated with the cTnI mutation than QTD.

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