Usefulness of surface electrocardiogram in predicting the clinical course of patients with hypertrophic cardiomyopathy

Fatih Bayrak, Gökhan Kahveci, Bülent Mutlu*, Muzaffer Değertekin, Ertan Demirtaş*

Department of Cardiology, Yeditepe University Hospital, Kozyatağı İstanbul,
*Department of Cardiology, Koşuyolu Heart and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Few data exist regarding the prognostic value of QT dispersion in hypertrophic cardiomyopathy (HCM). In this study, we prospectively investigated the association between baseline QT dispersion and clinical course of HCM.

Methods: Overall, 101 patients with asymmetric septal hypertrophy (59 men, mean age 45±16 years, range 13-74 years) were included in the study and were followed up for 595±367 days for clinical endpoints defined as cardiac death and hospitalization due to worsening in heart failure symptoms. QRS duration, QT interval, and JT interval were manually measured on 12-lead electrocardiogram (ECG). QT dispersion and corrected QT dispersion were calculated accordingly. The ECG findings of the patients with and without clinical endpoints were compared.

Results: Twenty-nine patients experienced clinical endpoints (3 sudden deaths, 26 hospitalizations due to worsening heart failure). The measurements of QT, JT and QRS intervals were all comparable between the two groups (p>0.05 for all). QT dispersion and corrected QT dispersion were significantly different between patients with and without clinical endpoints (64±30 ms vs. 83±18 ms and 71±33 ms vs. 90±18 ms, respectively, p=0.001 for both). Corrected QT dispersion >80 ms detected patients with clinical endpoints with sensitivity and specificity of 79% and 75%, respectively. Patients with corrected QT dispersion <80 ms were significantly free of clinical endpoints.

Conclusion: In conclusion, for patients with hypertrophic cardiomyopathy, measurement of baseline corrected QT dispersion from surface ECG may be used to identify those at risk for clinical deterioration at long-term follow-up. *(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 178-81)*

Key words: hypertrophic cardiomyopathy, QT dispersion, prognosis

Introduction

Hypertrophic cardiomyopathy (HCM), is a relatively common genetic disease. Patients with HCM may suffer adverse clinical events, including sudden death in the young and disability due to heart failure at any age (1, 2).

In most patients the surface electrocardiography (ECG) is abnormal, showing the feature of left ventricular hypertrophy and/or nonspecific ST changes with Q waves in inferior leads. Ambulatory Holter electrocardiogram (ECG) monitoring (3), signal-averaged ECG (4), QT dispersion (QTd) (5-8) and T-wave alternans (9) have been used previously as noninvasive prognostic tools in the evaluation and risk stratification of HCM patients. These studies focused on sudden cardiac death as an outcome and the results of various prognostic studies have been conflicting. However, little information is available regarding the use of these tools in predicting the clinical course of patients with HCM.

The purpose of the present study was to assess the association between baseline QT dispersion and clinical course of HCM.

Methods

Study population

Overall, 101 consecutive patients with asymmetric septal hypertrophy (59 men, mean age 45±16 years, range 13-74 years) were prospectively included in the study. The diagnosis of HCM was based on the demonstration of a hypertrophied, non-dilated left ventricle (wall thickness of at least 15 mm) by two-dimensional echocardiography in the absence of another cardiac or systemic disease capable of producing a similar degree of hypertrophy (10). A detailed clinical evaluation and baseline surface ECG recordings were obtained for each patient after the echocardiographic examination. Functional capacity was assessed according to the New York Heart Association (NYHA) classification by one investigator without knowledge of the laboratory results. Age and gender matched 30 control subjects were also included into the study. Patients with co-morbid cardiovascular, pulmonary, or renal conditions and patients with concentric, isolated posterior and apical hypertrophy were excluded from the study. The study protocol was approved by the local ethical committee and each patient gave written informed consent.

Echocardiographic analysis

A complete echocardiographic examination was performed with a Vivid Five System (GE, Vingmed Ultrasound, Horten, Norway) in each patient at rest by a single blinded observer. Left ventricle (LV) hypertrophy was assessed with 2-dimensional echocardiography according to published criteria (10). The greatest thickness measured at any site in the LV wall was considered to represent LV maximal wall thickness (11) Peak instantaneous LV outflow gradient was estimated under basal conditions with continuous wave Doppler (2). Echocardiographic

Address for Correspondence: Fatih Bayrak, MD, Department of Cardiology, Yeditepe University Hospital, Kozyatağı, İstanbul, Turkey
Phone: +90 216 578 42 44 Fax: + 90 216 578 49 63 E-mail: dfatihbayrak@yahoo.com

2D measurements included LV end-diastolic and end-systolic dimensions, posterior wall thickness, interventricular septal thickness, and LV ejection fraction. Pulsed Doppler was used to record mitral and tricuspid inflow patterns at the leaflet tips in the apical 4-chamber view. Mitral inflow Doppler was measured in standard fashion to determine peak E- and A-wave velocities, deceleration time of the transmitral E wave, and isovolumic contraction and relaxation times (12).

Electrocardiographic analysis

The ECG recordings were taken with a paper speed of 50 mm/sec at normal filtering. Several ECG parameters were measured manually. QRS duration was defined as the maximum QRS duration in any lead from the first to the final sharp vector crossing the isoelectric line. QT interval was measured from the lead II using calipers. QT interval was defined as the interval between the beginning of QRS complex and the end of T wave. The onset and offset of T wave were defined as the intersections of the isoelectric line and the tangent of the maximal slope on the up and down limbs of T wave, respectively. Care was taken to avoid U waves in any measurement, and when U waves were present, the end of T wave was taken as the nadir between T and U waves. Three consecutive cycles were measured in each of the standard 12 leads, and a mean value was calculated from the three values. The JT interval was then calculated by subtracting QRS from QT in individual leads. Bazett's formula was used to obtain corrected QT and these were represented as QTc. The dispersion of QT intervals was defined as the difference between the maximum and minimum of QT interval which could be measured in any of the 12 ECG leads and was represented as QTd. At the time of QT evaluation, all patients were hemodynamically stable and none had electrolytic disturbances, atrial fibrillation or significant intraventricular conduction defects.

Follow-up and study endpoints

Patients were prospectively followed-up to assess the value of ECG parameters for predicting the clinical course of HCM. The follow-up protocol included a clinical examination and a 12-lead electrocardiography performed at one-year intervals in an outpatient clinical setting. Patients who had not been seen for a year were contacted by telephone. The clinical endpoints were defined as a composite of cardiovascular death (sudden death, death due to worsening HF, cerebrovascular accident and death following interventional therapies), and hospitalization due to worsening of HF symptoms (progression to NYHA Class III or IV).

Statistical analysis

Statistical analysis was performed with SPSS 11.5 (SPSS, Chicago, Illinois, USA) software. Data are expressed as mean±SD or median based on whether they have a normal distribution or not. Statistical significance was taken as $P<0.05$. Relevant relationships were tested by χ^2 analysis for proportions and unpaired Student's t test for continuous variables. The statistical relationship between ECG parameters and other relevant demographic and echocardiographic variables such as age, LV outflow gradient and LV maximum wall thickness were first examined by Spearman's correlation, whereas variables such as gender and family history of sudden death were assessed by t tests.

Receiver operating characteristic (ROC) curves were used to select a QT dispersion cutoff value, which separated two groups of patients at low and high risk of clinical endpoints respectively. The event free survival rates of the risk groups were then estimated and compared using the Kaplan-Meier method.

Results

Patient characteristics

One hundred and one patients with HCM were compared with 30 age and gender matched controls. All 101 of HCM patients had asymmetric septal hypertrophy (ratio of end-diastolic septal to LV posterior wall thickness ≥1.5) and 48 patients (47%) had basal resting or exercise induced LV outflow tract obstruction with a peak gradient >30 mmHg. Thirty three patients (32%) had a positive family history of HCM and 23 patients (22%) had a history of sudden death in first degree relatives. Eighty-four patients (83%) were treated with beta blockers and 12 (11%) with calcium channel blockers. At admission 36 (35%) of the patients were asymptomatic (NYHA class I).

The comparison of demographic, echocardiographic and ECG variables of HCM patients and the control subjects are presented in Table 1. As expected, HCM patients had smaller LVs, thicker interventricular septal thickness and LV posterior walls, increased LV ejection fractions and longer E wave deceleration time and isovolumetric relaxation times than controls.

Mean follow-up period was 595±367 days (range 31 to 1142 days). Of the 29 patients (28%) with a clinical endpoint, 3 (3%) died of sudden death, 26 (25%) were hospitalized due to worsening of heart failure symptoms (11 patients with baseline NYHA Class II, and 15 with baseline NYHA Class III were hospitalized due to worsening of heart failure).

Table 1. Comparison of baseline clinical, demographic and echocardiographic variables of patients

Variables	HCM n=101	Control n=30	p
Demographics			
Female gender, n (%)	40 (46%)	8 (40%)	NS
Age, years	45±16	40±16	NS
Blood pressure, mmHg	116/67	113/64	NS
Echocardiographic variables			
Left atrium, mm	45±7	33±4	0.0001
LV end-diastolic diameter, mm	43±6	47±3	0.0001
LV end-systolic diameter, mm	24±6	32±2	0.0001
Septum diastolic thickness, mm	23±6	9±1	0.0001
Posterior wall diastolic thickness, mm	13±6	9±1	0.0001
Mitral E velocity, m/s	0.77±0.2	0.8±0.19	NS
Mitral A velocity, m/s	0.76±0.2	0.8±0.11	NS
E deceleration time, ms	223±76	190±23	0.001
IVRT, ms	109±30	89±10	0.0001
LV ejection fraction, %	75±8	69±5	0.0001
ECG variables			
QRS, ms	120±26	89±13	0.0001
QT, ms	361±64	350±53	NS
QTd, ms	70±21	33±18	0.0001

ECG- electrocardiogram, HCM- hypertrophic cardiomyopathy,
IVRT- isovolumetric relaxation time, LV- left ventricle, NS- not significant, QTd- QT dispersion

Anatol J Cardiol 2007: 7 Suppl 1; 178-81
Anadolu Kardiyol Derg 2007: 7 Özel Sayı 1; 178-81

Electrocardiographic comparison of HCM patients with and without clinical endpoints

The measurements of maximum QT, JT and QRS intervals were all comparable between the two groups (p>0.05 for all). QT dispersion (QTd) and corrected QT dispersion (QTcd) were significantly different between patients with and without clinical endpoints (64±30 ms vs. 83±18 ms and 71±33 ms vs. 90±18 ms, respectively, p=0.001 for both) (Table 2).

Corrected QT dispersion weakly correlated with NYHA functional class (r=0.2, p=0.03) and various echocardiographic parameters such as left atrium diameter (r=0.2, p=0.04), diastolic septum thickness (r=0.2, p=0.05), diastolic posterior wall thickness (r=0.2, p=0.05).

We examined the sensitivity and specificity of various cutoff values of corrected QT dispersion for predicting clinical endpoints and created ROC curves. The best value of QTcd with the highest sensitivity (79%) and specificity (75%) was 80 ms. Then, HCM population was stratified into low-, and high-risk subgroups by using QTcd cutoff of 80 ms. Patients with corrected QT dispersion <80 ms were significantly free of clinical endpoints during follow-up period (Fig. 1).

Discussion

The major finding of this study is that baseline QT dispersion was significantly increased in HCM patients who died suddenly or in patients who had clinical evidence of worsening heart failure symptoms at long-term follow-up. QT dispersion correlated with NYHA functional class, left atrium diameter, diastolic interventricular septum thickness, and diastolic posterior wall thickness. Patients with higher functional classes and more severe LV hypertrophy had higher QT dispersion values, which may explain the association between clinical deterioration and QT dispersion prolongation.

QT dispersion may provide a measure of myocardial repolarization inhomogeneity (13). Many experimental and clinical studies have demonstrated that increased QT dispersion contributes to the triggering of spontaneous malignant ventricular arrhythmia and sudden cardiac death in patients hypertrophic cardiomyopathy (5), or chronic heart failure (14-16).

Currently available studies report controversial results regarding QTd and prognosis in HCM. QTd (5) and QT prolongation (6, 17) have been reported in HCM previously. In a study of Buja et al. (5), QT interval and QTd were found to be significantly prolonged in HCM with ventricular tachyarrhythmia. On the other hand, Fananapazir et al. (17) stated that prolongation of both the QT interval and QTd were the common findings in patients with HCM and may not be of prognostic significance in the absence of syncope or cardiac arrest. Maron et al. (7) found that QT dispersion has no prognostic value in term of sudden death in patients with HCM. Goktekin et al (8) have shown no prognostic information from QTd regarding risk factors for sudden cardiac death in patients with HCM.

Hypertrophic cardiomyopathy carries risk for sudden death in young people, but is also an important cause of heart failure-related disability and death. Exertional dyspnea typically occurs in the presence of a normal systolic function in the context of impaired diastolic function (18). Carvalho et al. (19) found that QTd changes were primarily due to changes in the intracardiac blood volume and acute reduction of ventricular volume decreases QTd in elderly subjects with heart failure.

In another study, Yee et al, (20) reported that QTd was prolonged with increasing afterload in healthy subjects. We suspected that increased afterload (LV outflow obstruction) without systolic dysfunction might cause QTd prolongation in our patients with HCM, but no significant correlation was detected between QTd and presence of LV outflow obstruction. Thus, the early detection and prevention of the progression of HCM to heart failure are important and essential in HCM patients (21). This study demonstrates that QTd and QTcd are significant predictors for the onset of heart failure symptoms in patients with HCM. It is possible that QTd represents a preclinical prognostic electrocardiographic tool for worsening heart failure symptoms at long-term follow-up in patients with HCM.

Because of the low rate of sudden death in HCM, the contribution of QTd to risk stratification of sudden death remains limited. Thus, it might be necessary to perform analysis on a larger scale in another series of studies. It might also be of value to examine how QTd would be affected by the subsequent treatment, including medical and interventional therapies

In conclusion, for patients with HCM, measurement of corrected QTd from baseline surface ECG may be used to identify those at risk for clinical deterioration at long-term follow-up.

Table 2. Comparison of surface ECG data of patients with and without clinical endpoints

Variables	CE +	CE -	p
QRS, ms	128±43	116±15	NS
QT, ms	361±64	362±51	NS
QTc, ms	478±56	465±43	NS
JT, ms	245±53	235±45	NS
QTd, ms	83±18	64±30	0.001
QTcd, ms	90±18	71±33	0.001

CE- clinical endpoints, ECG- electrocardiogram, HCM- hypertrophic cardiomyopathy, NS- not significant, QTcd- QT corrected interval dispersion, QTd- QT dispersion

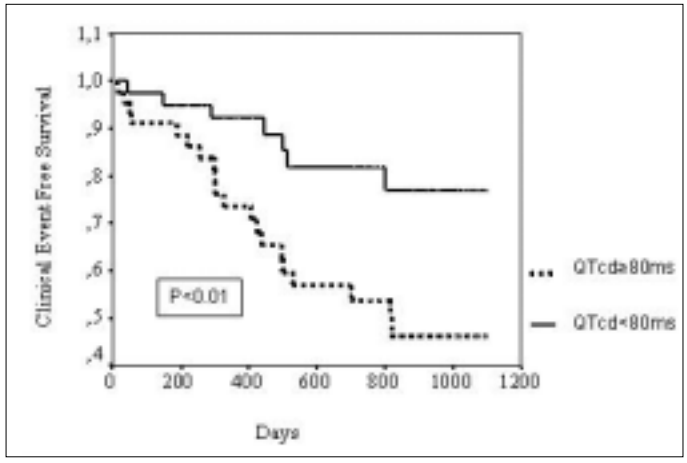

Figure 1. Kaplan-Meier survival curves of clinical endpoint free survival rates of patients with hypertrophic cardiomyopathy divided into 2 groups according to QTcd value

QTcd - QT corrected interval dispersion

References

1. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2003; 42: 1687-713.
2. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003; 348: 295-303.
3. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol 2005; 45; 697-704.
4. Fauchier JP, Fauchier L, Babuty D, Cosnay P. Time-domain signal averaged electrocardiogram in nonischemic ventricular tachycardia. Pacing Clin Electrophysiol 1996; 19: 231-44.
5. Buja G, Miorelli M, Turrini P, Melacini P, Nava A. Comparison of QT dispersion in hypertrophic cardiomyopathy between patients with and without ventricular arrhythmias and sudden death. Am J Cardiol 1993; 72: 973-6.
6. Yi G, Elliott P, McKenna WJ, Prasad K, Sharma S, Guo XH, et al. QT dispersion and risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy. Am J Cardiol 1998; 82: 1514-9.
7. Maron BJ, Leyhe MJ 3rd, Casey SA, Gohman TE, Lawler CM, Crow RS, et al. Assessment of QT dispersion as a prognostic marker for sudden death in a regional nonreferred hypertrophic cardiomyopathy cohort. Am J Cardiol 2001; 87: 114-5.
8. Goktekin O, Ritsushi K, Matsumoto K, Hiroshi M. The relationship between QT dispersion and risk factors of sudden death in hypertrophic cardiomyopathy. Anadolu Kardiyol Derg 2002; 2: 226-30.
9. Kuroda N, Ohnishi Y, Yoshida A, Kimura A, Yokoyama M. Clinical significance of T-wave alternans in hypertrophic cardiomyopathy. Circ J 2002; 66: 457-62.
10. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995; 26: 1699-708.
11 Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy predicts the risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000; 342: 1778-85.
12. Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. Circulation 2001; 104: 128-30.
13. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J 1990; 63: 342-4.
14. Davey PP, Bateman J, Mulligan IP, Forfar C, Barlow C, Hart G. QT interval dispersion in chronic heart failure and left ventricular hypertrophy: Relation to autonomic nervous system and Holter tape abnormalities. Br Heart J 1994; 71: 268-73.
15. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994; 343: 327-9.
16. Grimm W, Steder U, Menz V, Hoffmann J, Grote F, Maisch B. Clinical significance of increased QT dispersion in the 12-lead standard ECG for arrhythmia risk prediction in dilated cardiomyopathy. Pacing Clin Electrophysiol 1996; 19 (Pt II): 1886-9.
17. Fananapazir L, Chang AC, Epstein SE, McAreavey D. Prognostic determinants in hypertrophic cardiomyopathy: Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiologic findings. Circulation 1992; 86: 730-40.
18. Maron BJ, Tholakanahalli VN, Zenovich AG, Casey SA, Duprez D, Aeppli DM, et al. Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. Circulation 2004; 109: 984-9.
19. de Carvalho FC, Consolim-Colombo FM, Pastore CA, Rubira MC, Meneguetti JC, Krieger EM, et al. Acute reduction of ventricular volume decreases QT interval dispersion in elderly subjects with and without heart failure. Am J Physiol Heart Circ Physiol 2005; 288: H2171-6.
20. Yee KM, Lim PO, Ogston SA, Struthers AD. Effect of phenylephrine with and without atropine on QT dispersion in healthy normotensive men. Am J Cardiol 2000; 85: 69-74.
21. Hiasa G, Hamada M, Saeki H, Ogimoto A, Ohtsuka T, Hara Y, et al. Cardiac sympathetic nerve activity can detect congestive heart failure sensitively in patients with hypertrophic cardiomyopathy. Chest 2004; 126: 679-86.