Paper

The relationship between angiotensin converting enzyme gene I/D polymorphism and QT dispersion in patients with hypertrophic cardiomyopathy

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Abstract

Introduction: Hypertrophic cardiomyopathy (HCM) is characterized by disorganized myocardial architecture, and may cause ventricular arrhythmias and sudden death. The angiotensin-converting enzyme (ACE) with two deletion alleles (DD genotype) has been proposed to be associated with increased myocardial collagen content. We evaluated QT dispersion (QTd), which reflects regional differences in ventricular repolarization, in HCM patient and controls among the three different ACE genotypes.

Materials and methods: Sixty-three patients with HCM and 20 healthy subjects were included in the study. QT parameters were measured from 12 lead electrocardiograms. ACE genotypes were determined from the DNA extracted from peripheral blood by a polymerase chain reaction (PCR) method. QT parameters were compared among the three ACE genotypes both in HCM patients and controls.

Results: Median ages were similar in HCM and control groups. QTd and corrected QTd (QTcd) were significantly greater in the HCM group compared with the controls. The frequencies of each genotype were similar in both groups. Although QTd and QTcd did not differ among the three genotypes in the control subjects, they were significantly greater in patients with DD genotype compared with other genotypes in the HCM group.

Conclusion: QTd and QTcd are increased in patients with HCM, especially in those with the DD genotype.

Introduction

Hypertrophic cardiomyopathy (HCM) is a disorder of the myocardium that causes cardiac hypertrophy that cannot be attributed to an evident cardiac or systemic cause.[1,2] The prevalence of HCM is estimated to be around 0.2% in general population. It is caused by mutations in the genes encoding proteins of the cardiac sarcomere and is inherited as an autosomal dominant trait.[1]

HCM has a wide spectrum of clinical presentations ranging from asymptomatic hypertrophy to refractory heart failure and sudden cardiac death. Sudden death is the most common mode of death with an overall annual mortality rate about 1%.[1] Sudden death is presumed to be due to ventricular tachycardia or fibrillation. Abnormalities of ventricular repolarization, which are possibly caused by characteristic findings of disorganized myocardial architecture, can be one of the triggers that induce lethal arrhythmias.[3] It is essential to identify the patients who are at a higher risk of such a serious complication.

QT dispersion (QTd), which reflects regional differences in repolarization, is a risk factor for the development of ventricular arrhythmias and sudden death in a variety of cardiac disorders.[4-7] Moreover, increased QTd has been found to be associated with symptomatic status and family history of sudden cardiac death in patients with HCM.[8]

The angiotensin-converting enzyme (ACE) genotype with two deletion alleles (DD genotype) has been shown to be associated with higher plasma and cardiac ACE and angiotensin-II concentrations,[9,10] and increased QTd.[11-13] The increase in QTd may in part be explained by regional heterogeneity of repolarization caused by angiotensin-II-induced increased myocardial collagen content. Moreover, the DD genotype has been associated with the severity of hypertrophy and risk of sudden death in patients with HCM.[11,14]

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In this study, we evaluated a possible relationship between ACE gene I/D polymorphism and QTd and corrected QTd (QTcd) in patients with HCM.

Materials and methods

Study population

Sixty-three patients with HCM and 20 healthy controls that belong to same ethnic group (all were White) were enrolled in the study. HCM was diagnosed in the presence of an end-diastolic left ventricular wall thickness greater than or equal to 13 mm in the absence of demonstrable hypertrophic stimulus such as hypertension or aortic stenosis. Maximum wall thickness was measured by standard two-dimensional and M-mode echocardiography. Patients with non-sinus rhythm, atrioventricular block, bundle branch block, coronary artery disease, and those on antiarrhythmic, ACE inhibitor, or angiotensin receptor blocker therapy and those who did not give consent to participate were excluded. Three patients had a family history of HCM in the HCM group. The study was supported by Ankara University Scientific Research Project Center. All patients and controls gave oral and written informed consent to participate.

ECG analysis

QT intervals were measured manually from the onset of QRS complex to the end of T wave on 12-lead surface electrocardiograms (ECGs) that were recorded at 50 mm/s speed. The end of the T wave was defined as the intersection of the isoelectric baseline and the maximum tangent line of the T-wave terminal limb when it was unclear. QT interval was corrected (QTc) according to Bazett's formula.[15] QTd and QTcd were calculated as the difference between their corresponding maximum and minimum values measured in at least eight leads. Electrolytes were in the normal range on the day of the ECG recording.

ACE polymorphism genotyping

DNA was extracted from peripheral blood. Angiotensin converting enzyme genotypes were determined by polymerase chain reaction (PCR).[16] We placed 0.1 µg DNA, 4 pM primer 1, 4 pM primer 2, 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl, 0.2 mM of each dNTP, 5% DMSO (dimethyl sulphoxide) and 1 unite Taq polymerase in a microfuge tube and covered this with mineral oil. Samples were denatured for 3 minutes at 93°C initially and then cycled 30 times through the following steps: 1 minute at 92°C, 1 minute at 57°C and 1 minute at 72°C. Finally, the samples were incubated again for 7 minutes at 72°C. Obtained PCR products then were loaded in 2% agarose gel and visualized by ethidium bromide staining. The insertion allele (I) was detected as a 490-bp (base pair) band and the deletion allele (D) was detected as a 190-bp band. During PCR, the preference of deletion allele synthesis to insertion allele synthesis may lead to mistyping of ID genotypes as DD.[17] So, samples with DD genotype were passed through a second PCR by using insertion-specific primer.

Statistical analysis

Statistical analyses were performed by the use of SPSS version 11.5 (SPSS Inc., Chicago, Illinois). Differences between categorical variables were assessed by chi-squared test. Because QT parameters did not show a normal distribution, these data were assessed by non-parametric tests and were expressed as median (interquartile range: IQR) and mean±standard deviation (SD). A Kruskal–Wallis test was used for the assessment of the differences in QT parameters in each of the three genotypes. When a significant result was found, a Mann–Whitney *U*-test with Bonferonni correction was used for multiple comparisons. A possible correlation between left ventricular maximum wall thickness and QT parameters in the HCM group was evaluated by Spearman correlation analysis. A chi-squared goodness-of-fit test was used to determine whether the observed genotype distribution was in Hardy–Weinberg equilibrium. Values of $p < 0.05$ were considered statistically significant. In post-hoc multiple comparisons of QTd and QTcd across the three genotypes, by using Bonferroni correction, *p*-values were considered significant if $p < 0.017$.

Results

Patient characteristics and QT parameters

Clinical characteristics and QT parameters are summarized in Table 1. There were no significant differences in age, heart rate or female/male ratio between two groups. However, minimum and maximum QT and QTc intervals, QTd and QTcd were significantly greater in patients with HCM compared with the controls.

ACE genotypes

All observed genotype frequencies were in Hardy–Weinberg equilibrium ($\chi^2_{df:1} = 1.032$, $p = 0.31$ for the HCM group; $\chi^2_{df:1} = 0.189$, $p = 0.66$ for control group). The distribution of II, ID, and DD genotypes were not different between two groups ($p = 0.42$, Table 2).

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Table 1
Clinical characteristics and QT parameters in patients with HCM and in normal controls.

	HCM (n = 63)	Control (n = 20)	p-value
Age, years			
median (IQR)	60.0 (23.0)	53.5 (12.8)	0.34
mean±SD	55.94±14.8	53.9±7.9	
Male/female	39/24	8/12	0.09
Heart rate, bpm			
median (IQR)	70.0 (17.0)	67.5 (14.5)	0.22
mean±SD	72.6±13.4	67.8±9.7	
QT_{min}, ms			
median (IQR)	390.0 (20.0)	370.0 (27.5)	0.003
mean±SD	393±29	373±25	
QT_{max}, ms			
median (IQR)	420.0 (40.0)	400.0 (45.0)	0.001
mean±SD	422±31	395±29	
QTd, ms			
median (IQR)	20.0 (20.0)	20.0 (10.0)	0.024
mean±SD	29±12	22±10	
QTc_{min}, ms			
median (IQR)	430.0 (50.0)	395.0 (32.5)	<0.001
mean±SD	426±35	394±21	
QTc_{max}, ms			
median (IQR)	460.0 (50.0)	420.0 (30.0)	<0.001
mean±SD	458±40	416±23	
QTcd, ms			
median (IQR)	30.0 (20.0)	20.0 (10.0)	0.012
mean±SD	32±15	23±11	

HCM, hypertrophic cardiomyopathy; IQR, interquartile range; QTd, QT dispersion; QTcd, corrected QT dispersion; SD, standard deviation.

Table 2
Comparison of ACE genotypes between HCM patients and normal controls.

	ACE genotypes			
	II	ID	DD	p-value
HCM, n (%)	8 (13)	34 (54)	21 (33)	0.42
Control, n (%)	5 (25)	9 (45)	6 (30)	

ACE, angiotensin-converting enzyme; HCM, hypertrophic cardiomyopathy.

The relationship between ACE genotypes and QT parameters

In the HCM group, age, maximum left ventricular wall thickness and heart rate were similar in all three ACE genotypes (Table 3). However, QTd and QTcd were significantly different among the genotypes (overall $p < 0.001$ for both; Table 3). Post-hoc analysis revealed that both QTd and QTcd were significantly greater in the DD genotype compared with the other genotypes (Figure 1).

Correlation analysis was used to evaluate a possible relationship between maximum wall thickness and QT parameters in the HCM group. There was no significant correlation between QT parameters and maximum wall thickness (all of the p-values >0.05; all of the r values <0.25).

In the control group, age (49±5, 56±6, and 55±11, for II, ID, and DD groups, respectively; p = 0.217), heart rate (73±11, 68±8, and 62±10 for II, ID, and DD groups, respectively; p = 0.208) and all of the QT parameters were similar in each genotype.

When clinical characteristics and QT parameters of the patients with DD genotype in HCM and control groups were compared, the age and heart rate were similar. In this analysis, QT_{max} (428±21 versus 407±16 ms, p = 0.029), QTd (38±10 versus 23±10 ms, p = 0.009), QTc_{min} (424±26 versus 395±21 ms, p = 0.023), QTc_{max} (465±29 versus 417±19 ms, p = 0.001) and QTcd (41±11 versus 22±12 ms, p = 0.003) were found to be significantly higher in the HCM group.

Discussion

In the present study we demonstrated that QTd and QTcd were significantly higher in the HCM group than in the control group; and DD genotype is a predictor for increased QTd and QTcd in patients with HCM.

Increased QTd is a risk factor for sudden death and ventricular arrhythmias in patients with preexisting cardiac diseases.[4-7] Although it reflects the regional heterogeneity of repolarization, the mechanism of increased QT dispersion in HCM is not yet clear. Some authors suggest that it may be related to the degree of left ventricular hypertrophy,[8] whereas others do not.[18,19] Cellular disarray and fibrosis, characteristic findings of HCM, may increase QT dispersion by virtue of regional differences in impulse propagation.[18]

One of the important findings in our study is that increased QTd and QTcd are noted only in the HCM group with the DD genotype. This finding may be pathophysiologically important in terms of the mechanism of arrhythmias. The ACE DD genotype has been reported to be a risk factor for severity of hypertrophy.[14,20,21] Tanriverdi *et al.* demonstrated that athletes with ACE DD

Table 3
Clinical characteristics and QT parameters in each ACE genotype in the HCM group.

	ACE genotypes			
	II (*n* = 8)	ID (*n* = 34)	DD (*n* = 21)	*p*-value
Age, years				
median (IQR)	49.0 (25.5)	63.0 (18.5)	51.0 (26.0)	0.19
mean±SD	53±14	59±12	52±18	
MWT, cm				
median (IQR)	1.95 (0.6)	1.70 (0.6)	1.90 (0.5)	0.30
mean±SD	1.95±0.27	1.78±0.42	1.83±0.36	
Heart rate, bpm				
median (IQR)	74.0 (39.5)	70.0 (13.5)	68.0 (24.0)	0.66
mean±SD	79±20	71±13	73±11	
QT_{min}, ms				
median (IQR)	380.0 (55.0)	400.0 (20.0)	390.0 (20.0)	0.69
mean±SD	390±36	396±33	390±18	
QT_{max}, ms				
median (IQR)	400.0 (50.0)	420.0 (40.0)	440.0 (20.0)	0.11
mean±SD	413±34	420±35	428±21	
QTd, ms				
median (IQR)	20.0 (0.0)	20.0 (20.0)	40.0 (10.0)	<0.001
mean±SD	23±7	24±11	38±10	
QTc_{min}, ms				
median (IQR)	435.0 (65.0)	430.0 (55.0)	430.0 (40.0)	0.54
mean±SD	441±40	424±38	424±26	
QTc_{max}, ms				
median (IQR)	455.0 (62.5)	460.0 (55.0)	460.0 (50.0)	0.43
mean±SD	466±51	451±44	465±29	
QTcd, ms				
median (IQR)	20.0 (7.5)	20.0 (15.0)	40.0 (10.0)	<0.001
mean±SD	25±15	28±14	41±11	

ACE, angiotensin-converting enzyme; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; MWT, maximum left ventricular wall thickness; QTd, QT dispersion; QTcd, corrected QT dispersion; SD, standard deviation.

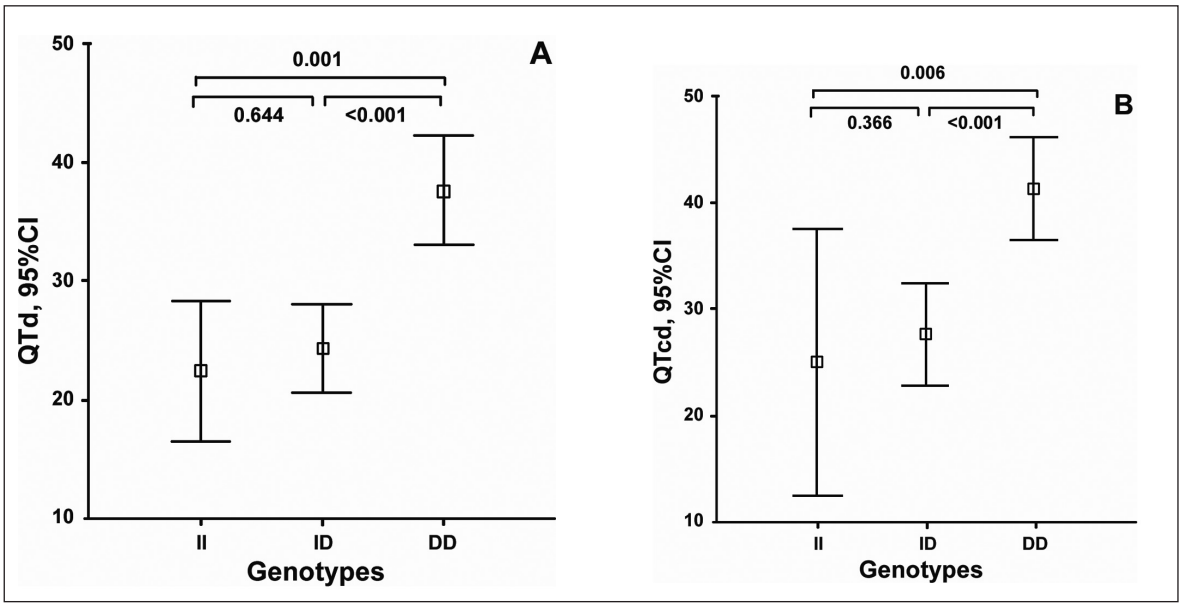


Figure 1
Comparisons of (A) QTd and (B) QTcd across the three genotypes in patients with HCM. Data are shown here as mean with 95% confidence interval. By using Bonferroni correction, *p*-values were considered significant if $p < 0.017$. HCM, hypertrophic cardiomyopathy; QTd, QT dispersion; QTcd, corrected QT dispersion.

genotype had greater left ventricular mass and increased QTd compared with the other genotypes.[22] One may speculate that the increased QTd and QTcd in our HCM patients with the DD genotype are caused by more severe left ventricular hypertrophy, however, maximum left ventricular wall thicknesses were similar among the three ACE genotypes in our HCM group. This result is consistent with that of Takahashi *et al.*, who demonstrated that ACE DD genotype was

associated with increased QTcd independent of the degree of left ventricular hypertrophy in patients with essential hypertension.[13] In our study, the absence of any association between increased QTd, QTcd and degree of left ventricular hypertrophy suggests other mechanism(s). One of the possible mechanisms may be myocardial fibrosis that is linked to the specific ACE genotype, as nicely demonstrated by Takahashi and colleagues.[13] Moreover, McLenachan and Dargie also demonstrated that ventricular arrhythmias in hypertensive patients with left ventricular hypertrophy were related to the degree of myocardial fibrosis.[23]

It has been proposed that myocardial fibrosis, scarring and disorganized architecture may favor ventricular reentry by local alterations in the electrical activity of the left ventricle.[1,24] Chronic elevations in angiotensin II and aldosterone levels provoke myocardial accumulation of fibrillar collagen.[25] The mechanism by which ACE DD genotype affects QTd and QTcd in our HCM group might be an increased amount of myocardial collagen caused by elevated angiotensin-II and aldosterone levels. Recently conducted cardiac magnetic resonance imaging (MRI) studies have shown that ventricular arrhythmias and sudden death were more prevalent in patients with fibrosis presenting as delayed gadolinium enhancement on cardiac MRI.[26,27]

We found that genotype frequencies were similar in patients with HCM and controls, and the effect of ACE DD genotype on QTd and QTcd was evident only in the HCM group. This may be explained by the concept of multiple genetic modifiers for a monogenic disease. The combination of ACE DD genotype and the underlying primary genetic defect leading to HCM may exaggerate the development of abnormal myocardial architecture and increase QTd and QTcd.[1,11,28] Increased levels of angiotensin-II and aldosterone levels caused by DD genotype may also affect the phenotypic expression in HCM. Therefore, our findings may suggest a possible synergistic effect between DD genotype and HCM in terms of increased QTd and QTcd, and possibly arrhythmogenesis in clinical ground. In a previous study, QT dispersion did not prove to be a reliable factor in determining sudden death risk in HCM.[29] However, the patients were not stratified according to ACE genotypes in that study.

Study limitations

Although it is not our primary aim, we compared the degree of left ventricular hypertrophy in each genotype to evaluate whether the relationship between DD genotype and increased QTd and QTcd is dependent on the degree of left ventricular hypertrophy. In this analysis we used maximum left ventricular wall thickness as an index of the degree of left ventricular hypertrophy. We think that the degree of left ventricular hypertrophy could be assessed more reliably by left ventricular mass calculation; however, left ventricular mass calculation from two-dimensional echocardiography using the Devereux formula may be misleading due to asymmetric hypertrophy. Magnetic resonance imaging or three-dimensional echocardiography could be used for this purpose. However, we think that this limitation does not change our primary finding of increased QTd and QTcd in HCM patients with DD genotype, but it may alter the finding that the effect of DD genotype on QTd and QTcd is independent of the degree of left ventricular hypertrophy.

We did not evaluate myocardial collagen content and plasma angiotensin-II, ACE or aldosterone levels in our patients. However, there are many studies demonstrating that DD genotype increases plasma and tissue angiotensin-II levels. For ethical reasons it seems impossible to conduct a study evaluating myocardial collagen content if there is no indication for endomyocardial biopsy. To the best of the authors' knowledge, there is only one study demonstrating that DD genotype is associated with an increased amount of carboxy-terminal propeptide of procollagen type I (PICP), a surrogate marker of interstitial fibrosis, in patients with hypertensive left ventricular hypertrophy.[30] As in our first limitation, this also has no effect on our primary finding, but may alter our hypothetical pathophysiological explanation.

Another limitation was that none of the patients were investigated for mutations in the disease genes, and hence we could have no idea about any possible correlation between the mutations and QTd in HCM patients. Further research is warranted to evaluate the effect of genetics on repolarization.

Finally, our study population size was relatively small. Therefore, elucidation of the underlying mechanism warrants further studies in a larger cohort of patients and control groups with more detailed genetic, biochemical and histological analysis.

Conclusion

This study demonstrated higher QTd and QTcd levels in HCM patients with DD genotype, but failed to show a relationship between the degree

of left ventricular hypertrophy and QT parameters. Risk stratification of sudden death in HCM remains a major challenge. The findings of the present study may add benefit to risk stratification strategies in patients with HCM and may encourage further research focusing on the effect of ACE DD genotype on QT dispersion, arrhythmogenesis and sudden death in HCM.

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