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Association Between ACE Gene Polymorphism and QT Dispersion in Patients with Acute Myocardial Infarction

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Abstract:

Background:

Angiotensin converting enzyme (ACE) gene polymorphism is associated with high renin-angiotensin system causing myocardial fibrosis and ventricular repolarization abnormality. Based on these findings, this study was designed to determine the association between ACE gene insertion/deletion (I/D) polymorphism and QT dispersion after acute myocardial infarction (MI).

Objective and Methods:

The study included 108 patients with acute MI. Blood samples were obtained from all the patients for genomic DNA analysis. ECGs were recorded at baseline and at the end of a 6-month follow up. The OT dispersion was manually calculated.

Results:

The mean age of the patients was 57.5 ±9.9 years (ranging from 36 to 70). The patients with DD genotype showed longer QT dispersion than patients with II or DI genotype at the baseline, while at the end of the six-month follow up the patients with DI genotype showed longer QT dispersion than patients with DD or II genotypes. However, the magnitude of the QT dispersion prolongation was higher in patients carrying the ACE D allele than patients who were not carrying it, at baseline and at the end of six-month follow up (52.5 ±2.6 msn *vs.* 47.5±2.1 msn at baseline, 57±3.2 msn *vs.* 53±2.6 msn in months, *P*: 0.428 and *P*: 0.613, respectively).

Conclusion:

Carriers of the D allele of ACE gene I/D polymorphism may be associated with QT dispersion prolongation in patients with MI.An interaction of QT dispersion and ACE gene polymorphism may be associated with an elevation of serum type I-C terminal pro-collagen concentration, possibly leading to myocardial fibrosis, and increased action potential duration.

Keywords: ACE gene polymorphism, Coronary artery disease (CAD), Myocardial infarction, QT dispersion.

INTRODUCTION

Angiotensin converting enzyme (ACE) is a member of the renin-angiotensin system (RAS) which converts angiotensin I to angiotensin II. Angiotensin II regulates vascular tone and controls blood pressure. The RAS is affected in coronary artery disease [1, 2].

The ACE insertion/deletion (I/D) polymorphism that affects the levels of ACE serum activity involves 287 base

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pairs in the intron 16 of the ACE gene [3]. ACE gene polymorphism determines the serum ACE levels. ACE levels are higher in the DD genotype than II and DI genotypes [4]. An I/D polymorphism of the ACE has been shown as a genetic marker for the risk of coronary artery disease (CAD) [5]. However, the D allele carriers are exposed to a higher level of angiotensin II, causing myocardial fibrosis and ventricular repolarization abnormalities, which plays an important role in the occurrence of cardiac arrhythmia [6].

QT dispersion has been associated with ventricular arrhythmias after MI and is considered an independent predictor of sudden cardiac death in MI [7]. The prolongation of QT dispersion is frequently associated with myocardial fibrosis severity after MI and is thought to show reduced ventricular repolarization homogeneity of a diseased heart [8].

The D allele carriers of ACE I/D gene polymorphism are shown to have higher levels of angiotensin II which is associated with poor prognosis after acute MI [9, 10]. In the present study, we investigated the relationship between ACE I/D gene polymorphism and QT dispersion in patients with acute MI.

Table 1. Baseline demographic and echocardiographic variables of the patients.

	DD genotype	II genotype	DI genotype	*P*
Number of Patients	29	20	59	0.22
Sex (Female/Male)	3/26	6/14	12/47	0.22
Mean Age (year) (± SD)	59.2 ±10	58.2 ±11	56.5 ±9.7	0.42
Hypertension	10	4	13	0.38
Diabetes Mellitus	4	3	6	0.81
Smoking	15	9	32	0.77
LV EF (%)	48.4 ±10	49.4 ±8	46.1 ±8.4	0.72
LV end-diastolic diameter (cm)	4.9 ±0.4	4.8 ±0.5	4.7 ±0.4	0.80
RV end-diastolic diameter (cm)	3.8 ±0.4	3.6 ±0.3	3.7 ±0.5	0.78

(LV EF, left ventricular ejection fraction)

METHODS

Patients

The study population consisted of 108 patients with acute MI (21 females and 87 males, with a mean age of 57.5 ±9.9 years) admitted to our clinic within six hours of the onset of chest pain. The diagnosis of MI was established according to the standard guidelines. Blood samples were obtained from all patients for genomic DNA analysis. The study was approved by the local Ethics Committee.

Echocardiography

The left and right ventricular end diastolic diameters were measured by echocardiography. The left ventricular ejection fraction was measured according to the modified Simpson method [11].

Electrocardiography

A standard 12 lead resting ECG was recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV at baseline. All ECGs were manually analyzed by a single experienced cardiologist blinded to the clinical data. Patients with complete bundle branch block, second or third degree atrioventricular block were excluded. The QT was defined as the interval between the QRS onset and the end of the T wave. QT dispersion was calculated as the maximal QT interval minus the minimal QT interval of the 12 leads.

Genetic Analysis

The genomic of the patients was isolated from peripheral blood leukocytes. The ACE gene polymorphism was analyzed by polymerase chain reaction and reverse hybridization with CVD Strip Assay (Vienna, Austria)**.**

Statistics

All data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using SSPS-18.0 (Statistical Package of Social Science version). Allele frequencies were deduced from the genotype frequencies. The differences in allele and genotype frequencies between the groups were evaluated by Mann-Whitney test and Kruskal Wallis test. Differences were considered significant for $P< 0.05$.

RESULTS

The study included 21 female and 87 male patients, and the age of patients at enrollment ranged from 36 to 70 years (mean 57.5 ± 9.9 years). In the 108 patients, 29 (26.9%), 59 (54.6%) and 20 (18.5%) patients had the ACE DD, DI and II genotypes, respectively. Additionally, 88 (81.5%) patients had the carriers of D allele gene. Table **1** presents the demographic and the echocardiographic data of all the patients. Moreover, there were no statistically significant differences between the three genotype groups and baseline characteristics.

Table 2. Association between ACE genotype and QT dispersion among the patients at baseline and after six months.

	DD genotype	II genotype	DI genotype	*P*
QT dispersion at baseline	54.8 ±2.5	47.5 ±2.1	51.4 ±2.6	0.611
QT dispersion after six months	55.2 ±3.3	53.1 ±2.5	57 ±3.1	0.842

The patients with DD genotype showed longer QT dispersi on than patients with II or DI genotype at the baseline. Whereas, the patients with DI genotype showed longer QT dispersion than patients with DD or II genotype at the end of the six-month follow up (Table **2**). On the other hand, the magnitude of the QT dispersion prolongation was higher in patients carrying the ACE D allele than not carrying the ACE D allele at baseline and the end of six-month follow up (Table **3**). But, there were no statistically significant differences between the three genotype groups and the D allele.

Table 3. Comparison of QT dispersion in patients with/without D allele carrier at baseline and after six months.

	D allele (+) n:88	D allele (-) n:20	*P*
QT dispersion at baseline	52.5 ±2.6	47.5 ±2.1	0.428
QT dispersion after six months	57 ±3.2	53 ±2.6	0.613

DISCUSSION

QT dispersion may contribute to an increased risk of ventricular arrhythmia and cardiac mortality. The prolongation of QT is frequently observed with age, medications, left ventricular hypertrophy and myocardial ischemia [12 - 14]. The left ventricular hypertrophy and myocardial infarction are known to reflect interstitial fibrosis that may result in prolonged action potential duration and QT dispersion [15]. The importance of QT dispersion is demonstrated in multiple studies [16]. In the present study, ACE I/D gene polymorphism may also affect QT dispersion in patients with diagnosed MI. We found that higher frequency of the D allele was also observed among the patients with acute MI. However, the patients with carrying the D allele had a higher prolongation of the QT dispersion at baseline and at the end of the six-month follow up.

Jeron *et al.*, have found that the D allele carriers are associated with higher serum and myocardial tissue ACE levels than the II allele carriers after MI [17]. Another study has also observed that ACE D allele carriers have a big dispersion prolongation [6]. Moreover, Cambien showed that a higher level of ACE in plasma could be a risk factor for MI independent of the the ACE I/D gene polymorphism [18]. It was previously shown that ACE I/D gene polymorphism might affect cardiac dilatation and hypertrophy in MI or hypertensive patients [10, 19, 20]. The DD genotype was also associated with left ventricular hypertrophy [21]. In patients with previous MI, Nagashi *et al.* found a significantly higher LV endsystolic and enddiastolic dimension in the deletion group [22]. Previous studies on the ACE I/D gene polymorphism with CAD have shown that the DD genotype is associated with increased risk of CAD [5, 23, 24]. A recent meta-analysis indicated that the ACE I/D polymorphism is related to an increased risk of MI [25] . In addition, the ACE I/D gene polymorphism has been extensively studied in cardiovascular and cerebrovascular diseases, such as ischemic stroke and coronary artery disease [26, 27].

Moreover, the carriers of DD genotype and the D alleles may affect the severity of CAD whereas the II allele carriers may have a protective effect [28]. The ACE genotypes were shown to be associated with prolongation of QT dispersion in previous studies [17, 29]. Although the precise mechanism of ACE I/D gene polymorphism and the QT dispersion is not well clear, the ACE D allele may be associated with high serum type I-C terminal procollagen concentration leading to myocardial fibrosis which increased action potential duration in some cardiac areas [30]. The present study indicates that the carriers of the D allele may affect the QT dispersion in patients with acute MI. But, there were no statistically significant differences between the three genotype groups and the D allele.

A limitation of the present study was the lack of long term follow up on the risk of cardiac arrhythmia and cardiac arrest and also relatively small sample size. In addition, the effects of gene-gene and gene-environment interactions

were not addressed in this study. Moreover, ACE plasma level was not measured, and it was influenced by many factors.

CONCLUSION

In patients with acute myocardial infarction, the carriers of D allele of ACE I/D gene polymorphism may be affected with the QT dispersion prolongation. Further studies are needed to support our results.

CONFLICT OF INTEREST

The authors confirm that this article contains no conflict of interest.

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