Relationship Between Angiotensin-converting Enzyme Gene Polymorphism and QT Dispersion in Hemodialysis Patients

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Introduction. The angiotensin-converting enzyme (*ACE*) gene insertion or deletion in long-term hemodialysis patients may be associated with corrected QT interval prolongation, leading to fatal arrhythmias. The *ACE* D allele is known to increase the risk of malignant ventricular arrhythmias and is also associated with increased QT dispersion after myocardial infarction and hypertension. This study aimed to evaluate the relationship between *ACE* gene polymorphism and QT dispersion in hemodialysis patients.

Materials and Methods. In 70 hemodialysis patients, electrocardiography was performed and QT dispersion was calculated. Corrected QT interval was calculated using Bazett Formula. The *ACE* gene polymorphism was determined by polymerase chain reaction.

Results. The mean age of the patients was 60 ± 12 years. The mean QT dispersion and corrected QT dispersion were 61.71 ± 21.99 and 73.18 ± 25.51, respectively. QT dispersion inversely correlated with serum calcium and potassium levels and positively correlated with *ACE* gene polymorphism and residual urine. Calcium level was the predictor factor for QT dispersion. The *ACE* genotype correlated with QT dispersion, corrected QT dispersion, hemoglobin, and residual urine, and inversely correlated with serum potassium. Corrected QT dispersion correlated with *ACE* gene polymorphism and residual urine. The DD genotype of *ACE* had significally greater QT dispersion and corrected QT dispersion than the II and ID genotypes.

Conclusions. Our study showed that the most important parameter affecting corrected QT dispersion was *ACE* gene polymorphism on the background of D allelle. Patients carrying this allelle need special attention regarding optimal suppression of renin-angiotensin-aldosteron system activity.

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INTRODUCTION

Cardiovascular diseases are the most common causes of mortality and morbidity in end-stage renal disease (ESRD) patients and responsible for half of deaths in long-term dialysis patients. Congestive heart failure, coronary artery disease, and sudden cardiac death are the main causes of cardiovascular deaths.[1,2] Mortality from arrythmias comprises 30% of all deaths in ESRD, notebly from the ventricular origin.

Hemodialysis patients exhibit a wide range of electrocardiographic abnormalities, especially

during and immediately after dialysis. Furthermore, hemodialysis procedure itself constitutes a major cause of electrocardiographic changes and arrythmias. On clinical grounds, different electrocardiographic parameters have been developed in order to anticipate the occurence of ventricular arrythmias.[3,4] QT interval dispersion is a measure of nonhomogenous ventricular repolarisation and recently mentioned as a predictive factor in life-threatening ventricular arrthmias.[5,6] QT dispersion is simply the interval difference between the shortest and the longest QT interval in a 12-lead electrocardiography.[7]

Numerous studies have been conducted to establish the relationship between the angiotensin-converting enzyme (*ACE*) gene polymorphism and cardiovascular diseases such as cerebrovascular and ischemic heart diseases, diabetes mellitus, and chronic kidney disease.[8] It has been shown that patients with *ACE* D/D genotype have high levels of ACE in plasma and heart and exhibit increased renal *ACE* mRNA expression.[9-11] It has also been verified that patients with D allele exhibit higher angiotensin II levels in comparison to those with I allele. Concordantly, rapid progression to ESRD, increased risk for myocardial infarction, malignant ventricular arrythmias, sudden cardiac death, and dilated cardiomyopathy have been observed in those with D allele.[12] D allele has been shown to be associated with increased QT dispersion in the postmyocardial infarction period and essential hypertension.[13,14]

This study aimed to investigate *ACE* gene polymorphism and increased QT dispersion in long-term hemodialysis patients. This would enable us predict those patients with adverse cardiovascular outcomes such as ventricular arrythmias.

MATERIAL AND METHODS

The study populaton consisted of 70 patients maintained on long-term hemodialysis, which was carried out thrice a week for a duration of 4 hours at the Department of Nephrology. On the day after the 2nd hemodialysis session, conventional 12-lead electrocardiography tracings were obtained in order to calculate QT dispersion values. The QT intervals were determined by taking the average value of 3 concecutive QT measurements in each electrocardiography derivation. Corrected QT intervals were calculated according to Bazzet formula (corrected QT = measured QT interval in seconds divided by the square root of R-R interval in seconds). QT and corrected QT dispersions were defined as the difference between maximal and minimal QT and corrected QT values were obtained from 12-lead measurements.

Peripheral venous blood samples of 1 mL were taken into the tubes with ethylenediaminetetraacetic acid and stored at -80°C. The *ACE* gene polymorphism was determined by a polymerase chain reaction method.

Patients with unmeasurable T waves, atrial fibrillation, and branch block pattern in electrocardiography as well as those taking any antiarrythmic or other class drug which could cause increased QT interval were excluded from the study.

All statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as median ± standard deviation. For correlation analysis involving numerical values, the Pearson bivariate test was used, whereas categorical data correlation analysis was conducted using the Spearman test.

RESULTS

The study population included 37 men and 33 women on long-term hemodialysis. The underlying etiologies of ESRD were diabetes mellitus in 25 (35.7%), hypertension in 19 (27.1%), obstructive uropaty in 8 (11.4%), polycystic kidney disease in 4 (5.7), tubulointerstitial nephritis in 4 (5.7), glomeulonephritis in 2 (2.9%), amyloidosis in 1 (1.4%), and unknown in 7 (10.0%). Thirty-two patients (45.7%) were hypertensive and 15 patients (22.9%) had cardiovascular diseases. Half of the patients were on antihypertensive treatment.

Demographic features and laboratory parameters as well as QT values of the patients are shown in Table 1. The patients were further divided on the basis of normal (< 65 msec) and prolonged QT dispersion; 41 patients were in the normal and 29 patients were in the prolonged QT dispersion subgroups, respectively. There was not any significant difference between the women and the men regarding the QT dispersion, corrected QT dispersion, or *ACE* polymorhism subgroups. There were significant correlations between *ACE*

Table 1. Demographic Features, Laboratory Parameters, and QT Values of the Study Population

Characteristic	Median Value	Range
Age, y	60.27 ± 12.97	28 to 84
Dialysis vintage, mo	16.15 ± 27.85	3 to 120
Hemoglobin, g/dL	10.00 ± 0.96	7.9 to 12.6
Blood urea, mg/dL	134.25 ± 64.20	39 to 337
Serum creatinine, mg/dL	5.71 ± 1.96	2.4 to 10.6
Serum calcium, mg/dL	8.59 ± 0.77	6.7 to 9.9
Serum potassium, mmol/L	4.41 ± 0.60	3.0 to 5.8
Serum magnesium, mg/dL	2.23 ± 0.45	1.4 to 3.0
Cardiothoracic ratio	50.21 ± 4.99	41 to 65
Residuel urine volume, mL	1621.92 ± 589.33	30 to 4300
QT max	418.28 ± 42.08	320 to 520
QT min	356.57 ± 35.54	280 to 440
QT dispersion	61.71 ± 21.99	40 to 120
Corrected QTmax	495.50 ± 48.62	400.0 to 623.4
Corrected QTmin	422.31 ± 42.73	320.0 to 571.4
Corrected QT dispersion	73.18 ± 25.51	40.0 to 155.4

gene polymorhism and QT dispersion (P = .008, r = 0.315) and *ACE* gene polymorphism and corrected QT dispersion (P = .007, r = 0.322). When the relationship was investigated between different ACE genotypes and QT dispersion and corrected QT dispersion values, the ID and DD subgroups, compared to the II subgroup, exhibited significant numbers and percentages of the patients belonged to increased QT dispersion and corrected QT dispersion subgroups (Table 2). The relationship between demographic features and laboratory parameters of the patients with normal and prolonged QT dispersion and corrected QT dispersion subgroups are shown in Table 3.

A logistic regression model was built including significant parameters affecting QT dispersion derived from binary statistical analyses. Serum calcium and potassium, residual urine, and *ACE* gene polymorphism were used in the model. The electrolytes influencing corrected QT and QT dispersion were in the desired ranges. The most significant parameter affecting QT dispersion was found to be calcium (β = -0.879, P = .04). The relationship between the demographic features and laboratory parameters and *ACE* gene polymorphism subgroups are shown in Table 4. The relationship between QT and corrected QT dispersion parameters and *ACE* gene polymorphism subgroups are shown in Table 5.

DISCUSSION

Hemodialysis patients have an increased risk of cardiovascular death as compared with the general population. Ventricular arrythmias or sudden death

Table 2. The Relationship Between *ACE* Gene Polymorphism Subgroups and QT Dispersion

QT Parameter	Patients With *ACE* Gene Polymorphism (%)			*P*
	II	ID	DD	
QT dispersion				
Normal	10 (24.4)	23 (56.1)	8 (19.5)	
Prolonged	0	18 (62.1)	11 (37.9)	.01
Corrected QT dispersion				
Normal	17 (53.1)	6 (18.8)	17 (53.1)	
Prolonged	24 (63.2)	13 (34.2)	24 (63.2)	.008

Table 3. The Relationship Between Demographic Features and Laboratory Parameters of the Patients and QT Dispersion and Corrected QT Dispersion Subgroups

	QT Dispersion			Corrected QT Dispersion		
Parameter	Normal	Prolonged	*P*	Normal	Prolonged	*P*
Age, y	59.56 ± 12.53	61.27 ± 13.72	.59	58.18 ± 12.80	62.02 ± 13.01	.22
Dialysis vintage, mo	15.82 ± 27.45	16.62 ± 28.89	.91	15.71 ± 27.11	16.52 ± 28.82	.91
Hemoglobin, g/dL	10.04 ± 0.93	9.95 ± 1.02	.70	9.97 ± 0.80	10.03 ± 1.09	.79
Blood urea, mg/dL	128.60 ± 60.34	142.96 ± 69.50	.36	129.15 ± 59.21	139.10 ± 68.58	.52
Serum creatinine, mg/dL	5.86 ± 2.21	5.50 ± 1.53	.46	5.72 ± 2.23	5.70 ± 1.72	.98
Serum calcium, mg/dL	8.69 ± 0.77	8.28 ± 0.53	.02	8.70 ± 0.78	8.37 ± 0.63	.06
Serum potassium, mmol/L	4.47 ± 0.62	4.19 ± 0.50	.05	4.45 ± 0.63	4.27 ± 0.54	.19
Serum magnesium, mg/dL	2.23 ± 0.35	2.08 ± 0.38	.09	2.25 ± 0.35	2.10 ± 0.37	.09
Cardiothoracic ratio	50.12 ± 5.71	50.34 ± 3.86	.86	50.31 ± 6.05	50.13 ± 3.98	.88
Residual urine volume, mL	1488.90 ± 559.76	1810 ± 587.99	.02	1443.28 ± 548.21	1772.36 ± 587.41	.02

Table 4. Relationship Between Demographic Features and Laboratory Parameters of the Patients and *ACE* Gene Polymorphism Subgroups

Parameter	*ACE* Gene Polymorphism			*P*
	II	ID	DD	
Age, y	58.30 ± 15.36	59.58 ± 12.38	62.78 ± 13.28	.62
Dialysis vintage, mo	24.70 ± 34.57	16.02 ± 26.19	11.94 ± 28.17	.14
Hemoglobin, g/dL	10.16 ± 0.71	9.77 ± 0.90	10.42 ± 1.10	.04
Blood urea, mg/dL	142.90 ± 46.62	135.12 ± 68.51	128.94 ± 64.88	.65
Serum creatinine, mg/dL	5.58 ± 2.33	5.80 ± 2.01	5.60 ± 1.71	.75
Serum calcium, mg/dL	8.52 ± 0.75	8.59 ± 0.69	8.37 ± 0.78	.47
Serum potassium, mmol/L	4.79 ± 0.46	4.30 ± 0.60	4.25 ± 0.52	.04
Serum magnesium, mg/dL	2.06 ± 0.26	2.23 ± 0.37	2.10 ± 0.38	.27
Cardiothoracic ratio	51.00 ± 6.71	50.14 ± 4.52	49.94 ± 5.22	.94
Residual urine volume, mL	864 ± 430.09	1602.19 ± 381.84	2069.42 ± 623.79	< .001

Table 5. The Relationship Between QT Dispersion and Corrected QT Dispersion Subgroups and *ACE* Gene Polymorphism Subgroups

Parameter	*ACE* Gene Polymorphism			*P*
	II	ID	DD	
QT dispersion	42.00 ± 6.32	63.90 ± 22.00	67.36 ± 22.32	.005
Corrected QT dispersion	50.03 ± 8.67	76.02 ± 26.48	79.24 ± 23.35	.004

are responsible for 64% of all cardiac deaths or 27% of all-cause mortality in hemodialysis patients.[15] Being an indirect measurement of ventricular repolarisation, QT dispersion reflects increased risk of ventricular arrythmias. Increased QT interval can be caused by a variety of factors such as left ventricular hypertrophy, hypertension, congestive heart failure, ischemic heart disease, diabetes mellitus, and specifically for ESRD patients drugs, acid base and electrolyte disturbances.

In our study, the average QT dispersion and corrected QT dispersion values were 61.71 ± 21.99 and 73.18 ± 25.51, respectively. There was not any relationship between sex and QT and corrected QT values. Similarly, in a study conducted by Raizada and colleagues, which was performed in hemodialysis patients, sex and QT and corrected QT interval did not show any relationship.[14,16] We could not show any significant relationship between demographic features and normal or prolonged QT dispersion subgroups. Significant inverse relationships were detected between calcium and potassium concentrations and QT dispersion. Because hypokalemia and hypocalcemia were well known causes of increased QT interval, this prolongating effect can be used as an explanation for the relationship between calcium and potassium concentrations and QT dispersion. In support of this explanation, Yelamanchi and colleagues verified the relationship between hypokalemia and increased QT dispersion and corrected QT dispersion and demonstrated that the treatment of hypokalemia resulted in the normalisation of QT dispersion and corrected QT dispersion.[17] Although Raizada and colleagues could not demonstrate a significant correlation between plasma electrolyte levels and corrected QT, normal plasma electrolyte levels and the small sample size of their study could account for this apparent lack of relationship.[16]

It has been demonstrated that RAS polymorphisms characterised by *ACE* DD genotype, *AT1R* C allele have been associated with left ventricular hypertrophy, myocardial fibrosis, and hypertension.[16,18] This can be explained by the prolonged ventricular repolarisation due to electrophysiologic remodelling of myocardium.[16]

Studies have shown that the patients experienced with hypertension or myocardial infarction, corrected QT interval and QT dispersion abnormalities have exhibited more pronounced and frequent with *ACE* DD genotype in comparison to those with *ACE* ID and II genotypes.[14,16] Kaya and colleagues demonstrated that *ACE* DD genotype was a predictor for increased QT dispersion and corrected QT dispersion in patients with hypertrophic cardiomyopathy.[19] In a study comprising 106 healthy elderly with an average age of 72.7 ± 4.1 years and a 4-year follow-up, Lin and colleagues showed the increased degrees of QT dispersion and corrected QT dispersion in a

subgroup with *ACE* DD genotype in comparison to other *ACE* genotypes.[20] In light of all those studies mentioned, given the facts that in our study *ACE* gene polymorphism was the mere factor correlating with corrected QT dispersion and being amongst the three factors effecting the QT dispersion together with plasma potassium and calcium concentrations, more pronounced degrees of QT and corrected QT dispersion in ESRD patients with DD genotype in comparison to II and ID genotypes, *ACE* DD allele can be considered a very strong risk factor for the occurence of ventricular arrythmias.

Cardiac myocytes from experimental models of renal failure have shown alterations in repolarizing potassium channels, due to the direct effects of uremia.[21] The repolarizing potassium channels are also abnormal in conditions associated with ESRD, such as hypertension, diabetes mellitus, anemia, chronic inflammation, and electrolyte abnormalities and acidosis.[14,21-25] Cardiac ion channels can be affected by such factors as the stretch of the myocytes by high blood pressure,[14,26] and the paracrine factors released from the nonmyocyte cells,[27] related to the excessive intermyocyte collagen and fibrosis in cardiac hypertrophy and uremia.[21,22,26] The changes in ion channels are accompanied by the reexpression of the fetal gene program.[26] Therefore, the corrected QT interval prolongation found in over half of our patients may be a marker of cardiac adaptation to numerous abnormalities unique to the ESRD and chronic hemodialysis. It is possible that the RAS overactivity associated with the *ACE* DD genotype intensifies the alterations in cardiac ion channels, resulting in a longer QT interval.

In our study a significant correlation was detected between *ACE* genotypes and plasma potassium concentration. Increased aldosterone levels consequent upon increased renin-angiotensin system activity might cause increased potassium secretion at the distal tubules thus causing a tendency toward hypokalemia. In harmony with this, patients having *ACE* DD genotype have lower plasma potassium concentrations in our study. When combined with the fact that *ACE* DD genotype was associated with more residual urine volumes in our patients, it seems logical to associate *ACE* DD genotype with increased renal potassium excretion. The cause of the association between increased residual function and *ACE* DD genotype might be salt and water retention in this context due to increased aldosterone activity. A practical support fort this assumption comes from different daily urine volumes of hemodialysis patients. After an hemodialysis session urine volume decreases but the day after hemodialysis residual urine volume increases.

The *ACE* DD genotype also causes increased sympathetic activity and high levels of tissue angiotensin II.[28,29] Renal hypoperfusion and ischaemia would be inevitable due to both of these factors. Chronic renal ischaemia causes increased erythropoetin secretion.[30,31] In support of this, in our study patients with *ACE* DD genotype have elevated hemoglobin levels in comparison to those with II or ID genotypes.

CONCLUSIONS

In uremic patients, cardiovascular mortality is seen 5 to 10 times more frequent in comparison to general healthy population. Classical cardiovascular risk factors could not account for this increased mortality entirely. Amongst the non-classical risk factors, QT dispersion is a prominent one. In this study, *ACE* gene polymorphism has been documented to be the most important factor effecting QT dispersion. As far as we know, in the studies performed to explain the causes of increased QT dispersion and corrected QT dispersion in ESRD patients, *ACE* gene polymorhism had not been included in the multivariable regression analysis. From these findings it can be deduced that various measures including ACE inhibitors and angiotensin receptor blockers to suppres ACE activty in chronic kidney failure patients with increased QT dispersion might be an important therapeutic modality in the future.

CONFLICT OF INTEREST

None declared.

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