The relationship between iron stores and corrected QT dispersion in patients undergoing hemodialysis

Hemodiyaliz hastalarında vücut demir depoları ile düzeltilmiş QT dispersiyonu arasındaki ilişki

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ABSTRACT

Objective: Cardiac arrhythmias commonly occur in hemodialysis patients. QT dispersion (QTd=QTmax-QTmin) reflects heterogeneity of cardiac repolarization, and increased QTd is known to predispose the heart to ventricular arrhythmias and sudden cardiac death. The aim of our study was to assess the association of iron stores, reflected by transferrin saturation (TSAT) and ferritin, with the dispersion of corrected QT intervals (QTc) in patients undergoing hemodialysis.

Methods: This cross-sectional, case-controlled study included 40 patients (23 men and 17 women) with renal failure undergoing hemodialysis (Patient group) and 27 subjects (10 men and 17 women) with normal renal function (Control group). In all patients and control subjects, QT intervals were measured on electrocardiogram, and QTc intervals and QTc dispersion were calculated. Electrolyte, hemoglobin and serum TSAT and ferritin levels were also determined.

Results: Hemodialysis patients had significantly greater QTc dispersion compared to that of control subjects (61.7±23.0 msec vs. 46.0±15.7 msec; p=0.001). Though serum iron levels were significantly associated with greater QTc dispersion (r=0.324, p=0.042), other electrolyte levels, duration of dialysis, TSAT and serum ferritin levels were not.

Conclusion: Although hemodialysis patients have greater QTc dispersion than control subjects, their levels of iron stores as reflected by TSAT and ferritin levels, does not correlate with the degree of QT dispersion. *(Anadolu Kardiyol Derg 2007; 7: 270-4)*

Key words: Iron intoxication, transferrin saturation, ferritin, QT interval, QT dispersion, QTc dispersion, hemodialysis

ÖZET

Amaç: Hemodiyaliz hastalarında kardiyak aritmilere sık rastlanılmaktadır. Kardiyak repolarizasyonun heterojenitesini yansıtan QT dispersiyonundaki (QTmax-QTmin) artışın, kalbi ventriküler aritmilere duyarlı hale getirdiği ve ani kalp ölümüne yol açabildiği bilinmektedir. Bu çalışmanın amacı hemodiyaliz hastalarında total vücut demirini yansıtan serum transferin satürasyonu (TSAT) ve ferritin ile bu hastaların düzeltilmiş QT dispersiyonu (QTc) ölçümleri arasındaki ilişkinin araştırılmasıdır.

Yöntemler: Vaka-kontrollü, kros-seksiyonel çalışmaya hemodiyaliz tedavisi altında olan böbrek yetmezlikli 40 hasta (23 erkek, 17 kadın) (Hasta grubu) ve böbrek fonksiyonları normal olan 27 birey (10 erkek, 17 kadın) (Kontrol grubu) alınmıştır. Tüm hastalara ve sağlıklı bireylere elektrokardiyografi ile QT ve QTc dispersiyonu ölçümleri yapılmıştır. Serum elektrolit, hemoglobin, TSAT ve ferritin seviyeleri de tayin edilmiştir.

Bulgular: Hemodiyaliz hastalarının QTc dispersiyonunun kontrol grubundaki bireylere kıyasla belirgin olarak artmış olduğu saptanmıştır (61.7±23.0'ye karşılık 46.0±15.7 ms; p=0.001). Serum demiri ile QTc dispersiyonu artışı arasında anlamlı ilişki tespit edilirken (r=0.324, p=0.042), serum elektrolit seviyeleri, diyaliz tedavisi süresi, TSAT ve serum ferritin düzeyleri ile QTc dispersiyonu artışı arasında anlamlı ilişki tespit edilememiştir.

Sonuç: Hemodiyaliz hastalarında QTc dispersiyonu kontrol bireylere göre arttığı, TSAT ve ferritin düzeyi ile yansıtılan serum demir depolarının QT dispersiyonunun derecesi ile ilişkisinin olmadığı sonucuna varılmıştır. *(Anadolu Kardiyol Derg 2007; 7: 270-4)*

Anahtar kelimeler: Demir zehirlenmesi, transferrin satürasyonu, ferritin, QT intervali, QT dispersiyonu, QTc dispersiyonu, hemodiyaliz

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and death in patients with end-stage renal disease (ESRD) treated by chronic hemodialysis (HD). Major aspects of CVD include a high prevalence of systemic arterial hypertension, ischemic heart disease, congestive heart failure, electrolyte disturbances, and arrhythmias (1).

The QT interval reflects the duration between the beginning of ventricular depolarization and the end of ventricular repolarization. Prolongation of the QT interval has been reported to be associated with arrhythmogenesis in a number of cardiac

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disorders (2). QT dispersion (QTd) is the variation in QT interval length (QTd=QTmax-QTmin) on a standard 12-lead electrocardiogram (ECG), and has been used as a marker of spatial variability in ventricular repolarization to identify patients at risk for ventricular arrhythmias (3, 4). The normal range for QTd is 40 to 50 ms with a maximum of 65 ms; values greater than 65 ms are associated with an increased risk of serious ventricular arrhythmias (5, 6). QTd is often elevated in patients with diabetes mellitus, left ventricular hypertrophy, myocardial infarction, familial long-QT syndrome and mitral valve prolapse (4, 5, 7-11).

Iron overload, from repetitive administration of parenteral iron or blood in attempts to maintain an optimum response to erythropoietin therapy, may increase the risk for cardiac death in patients with ESRD (12). The toxicity of iron in biological systems is believed to be associated with its ability to catalyze the generation of free radicals (13). Iron-induced cardiomyopathy is a restrictive cardiomyopathy that manifests as systolic or diastolic dysfunction and/or ventricular arrhythmias secondary to increased deposition of iron in the myocardium. Elevated levels of iron in the myocardium may cause QT prolongation and thereby increase the risk for arrhythmias (14, 15).

In this study, we evaluated the association between QT dispersion and iron load, as measured by serum ferritin and transferrin saturation (TSAT) in patients undergoing regular HD.

Methods

After the study was approved by the Ethics Committee of our medical faculty, a convenience sample of 49 hemodialysis patients older than 18 years old with a dialysis duration of at least 3 months, and dialysis frequency of at least three times per week were approached about entering the study between June and September 2005. After giving written informed consent to participate, they underwent a history and physical and had an ECG performed.

Patients were excluded if they had diabetes mellitus (n=3), chronic atrial fibrillation (n=4), or bundle branch block (n=2).

The remaining 40 patients (23 men and 17 women, mean age 49±17 years), who had a mean duration of hemodialysis of 31±30 months, continued with the study protocol. Nineteen patients were using anti-hypertensive (calcium channel- and/or beta-blocking agents) or antianginal medications. As part of our dialysis program's routine protocol, HD patients were prescribed parenteral iron supplements when their ferritin levels were less than 100 ng/mL or their TSAT was less than 20% (n=14). Patients with a hemoglobin level less than 10 g/dL had been prescribed erythropoietin (n=24).

Twenty-seven control subjects over the age of 18 (10 men and 17 women, mean age 44±11 years), who were normotensive and had normal renal function (serum creatinine levels less than 1.4 mg/dL), were recruited on a volunteer basis from our 'check-up clinic' to participate in the study and underwent identical examination and testing. Neither patients nor control subjects were receiving class I or class III antiarrhythmic or tricyclic antidepressant medications.

Study design

The study design was cross-sectional and case-controlled. The sample size of the study was calculated at significance level of 5% and power of the study of 80%.

Blood tests

Blood for routine electrolyte and iron profile (iron, total iron binding capacity, ferritin, transferrin saturation) tests was drawn when coming to our center, before dialysis was performed. The corrected calcium was calculated by adding 1mg/dL to the measured serum calcium level for every 1g/dL decrease in serum albumin level, when the serum albumin level was below 4.0 g/dL (16). Transferrin saturation was calculated by dividing the serum iron concentration by the total iron-binding capacity.

Measurement of QTc dispersion

Twelve-lead ECGs were obtained for all patients and control subjects at 10 mm/mV and 50 mm/s (ECG-9320 K, Nihon Kohden Corporation, Tokyo, Japan) after resting for 10 minutes. The ECGs of the HD patients were performed at the end of the dialysis session. All ECGs were analyzed manually with calipers by a single observer who was blinded to all clinical data. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, at the point where the T wave returned to the TP baseline. If the T wave was flat or could not be clearly determined, the lead under examination was excluded from analysis. At least nine leads on each ECG were measurable in all cases. The average QT interval was calculated from that of three successive heart cycles in each lead. The R-R interval from the preceding cardiac cycle was measured from the peaks of the R waves to correct the QT interval (QTc) for the heart rate using Bazett's formula: $QTc=QT/(R\text{-}R)^{1/2}$ where R-R is the RR interval in seconds (17). QTc dispersion, the difference between the maximum and minimum QTc intervals, was calculated. All ECGs were performed at the same time of day in all patients in order to minimize the effect of the diurnal pattern on QT interval (18).

QT measurement reliability

To assess the observer reliability of QTc dispersion measurements, fifteen ECG records were randomly chosen for re-measurement of the QT intervals two months after the initial measurements. The researcher was blinded to all clinical data. The mean difference in measured QT intervals was 1.4 ms (65.5±28.5 ms and 64.1±28.6 ms) with a correlation coefficient of 0.987 ($p<0.001$).

Statistical analysis

Comparisons between groups were made using Student's t-test, Mann-Whitney U test, Chi-square test and Pearson correlation tests. A $p<0.05$ was considered to be statistically significant. Linear regression analysis was used to determine the relationship of QTc dispersion with the markers of iron levels in the HD group. Statistical analyses were performed using SPSS version 10.0 for Windows (SPSS Inc., Chicago, USA) software.

Results

In the HD patients, chronic glomerulonephritis (22.5%) and polycystic kidney disease (20%) were the most common causes of ESRD (Table 1). Demographic, clinical, and baseline laboratory data from both HD and control groups are shown in Table 2. Importantly, differences in age, mean arterial pressure, and corrected serum calcium were not significantly different between HD patients and control subjects. Serum magnesium, TSAT and serum ferritin levels were significantly higher in HD patients than that of the control subjects ($p<0.001$).

Table 1. Clinical data, medication use, and causes of end-stage renal disease in the hemodialysis patient group

Age, years	48.9±16.7
Gender (F/M), n	17/23
Duration of hemodialysis, months	30.9±30.4
Parenteral iron supplements, n(%)	14 (35)
Recombinant human erythropoietin, n(%)	24 (60)
Antihypertensive medications, n(%)	19 (48)
Chronic glomerulonephritis, n(%)	9 (22.5)
Polycystic kidney disease, n(%)	8 (20)
Hypertensive nephropathy, n(%)	6 (15)
Reflux nephropathy, n(%)	4 (10)
Chronic tubulointerstitial nephritis, n(%)	2 (5)
Secondary amyloidosis, n(%)	2 (5)
Post-nephrectomy, n(%)	1 (2.5)
Lupus nephritis, n(%)	1 (2.5)
Unknown, n(%)	7 (17.5)

Table 2. Demographic, clinical, and laboratory data of hemodialysis and control subjects

Parameters	HD patients (n = 40)	Controls (n = 27)	p*
Sex (M/F), n	(23/17)	(10/17)	NS
Age, years	49±17	44±11	NS
Heart rate, beats/min	82±14	71±13	0.003
Mean arterial pressure, mm Hg	96±15	94±15	NS
Blood urea nitrogen, mg/dL	64±25	13±4	<0.001
Serum creatinine, mg/dL	9.2±3.0	0.9±0.1	<0.001
Albumin, mg/dL	3.7±0.6	4.3±0.2	<0.001
Corrected calcium, mg/dL	9.2±0.8	9.2±0.4	NS
Sodium, mEq/L	140±2	143±2	<0.001
Potassium, mEq/L	5.6±1.0	4.3±0.3	<0.001
Phosphate, mg/dL	5.3±1.7	3.5±0.5	<0.001
Magnesium, mg/dL	2.6±0.5	2.2±0.2	<0.001
Iron, µg/dL	96±60	76±35	NS
Total iron binding capacity, µg/dL	231±61	358±39	<0.001
Transferrin saturation, %	41±22	21±10	<0.001
Ferritin, ng/mL	1473±657	71±11	<0.001

Data are presented as Mean±SD
*- p values significance by Student t unpaired test and Mann-Whitney test
HD-hemodialysis, NS - not significant.

The QTc interval measurements of HD patients and control subjects are shown in Table 3. Although the mean QT interval was not significantly different between HD patients and control subjects, HD patients had a significantly longer QTc dispersion (62±23 ms vs. 46±16 ms, p=0.001). Ten (25%) of the HD patients, but only one control subject (3.7%) had a QTc dispersion of greater than 65 ms. The mean QT intervals of controls and HD patients whose serum creatinine level was less than 1.4 mg/dL were similar (p=0.82).

For HD patients, correlation was low between QTc dispersion and hemoglobin level, electrolyte levels, mean arterial pressure, and duration of HD treatment (Table 4). However, higher serum iron levels (but not TSAT) were significantly and positively associated with greater QTc dispersion (r=0.324, p=0.042). When HD patients were grouped according to QTc dispersion of >65 ms (n=10) or ≤65 ms (n=30), mean TSAT and serum ferritin levels were not significantly different (p = 0.179 and p = 0.901, respectively).

Discussion

Our study demonstrates that QTc interval dispersion is increased in ESRD patients undergoing chronic hemodialysis as compared with control subjects. Patients with renal failure also had higher levels of serum magnesium, TSAT and serum ferritin than persons with normal renal function. However, we could not find any significant relationship between QTc dispersion values and TSAT and serum ferritin levels in our hemodialysis patients.

Hemodialysis patients, who frequently consume iron supplements, are known to have a higher rate of cardiac dysrhythmias (3). Myocardial iron deposition and injury are

Table 4. Correlation between QTc dispersion and clinical and laboratory data in hemodialysis patients

	QTc dispersion, ms	
	r	p
Duration of hemodialysis, months	0.004	0.978
Mean arterial pressure, mm Hg	0.284	0.075
Hemoglobin, mg/dL	-0.019	0.907
Sodium, mEq/L	-0.240	0.135
Magnesium, mg/dL	0.071	0.686
Phosphate, mg/dL	0.067	0.685
Iron, µg/dL	0.324	0.042
Transferrin saturation, %	0.285	0.075
Ferritin, ng/mL	-0.079	0.629

Table 3. Mean values of QT interval and QTc dispersion in hemodialysis and control subjects

Parameters	HD Patients (n=40)	Range	Controls (n=27)	Range	p*
QT interval, ms	388±33	320-480	387±23	330-420	0.909
QTc dispersion, ms	62±23	23-121	46±16	23-84	0.001

Data are presented as Mean±SD,
* - p values significance by Student t unpaired test and Mann-Whitney test
HD-hemodialysis

regarded as major determinants of survival in patients with secondary iron overload (19). The TSAT and serum ferritin are often measured to determine the iron status of patients. To date, only one study has been published regarding the association of iron status with QTc dispersion in ESRD patients. Wu et al (14) measured QTc dispersion along with TSAT and ferritin levels in 102 peritoneal dialysis patients and found a linear correlation between QTc with TSAT and serum ferritin levels, as well as a direct relationship between the duration of PD therapy and magnitude of QTc dispersion (14).

Our conflicting results on the absence of such a relationship between QTc dispersion and TSAT and ferritin levels may be due differences in our patient population - we studied hemodialysis patients, whose QT dispersion may be affected to a greater degree of changes in the myocardium caused by the sharp electrolyte changes, which occur during hemodialysis (15). Thus, even if a clear correlation existed between QTc dispersion and iron stores in ESRD patients, it may be impossible to demonstrate such a relationship in HD patients. Although we found a correlation between QTc dispersion and serum iron, 35% of our patients were taking supplemental iron, which can affect the actual serum iron levels at the time of measurement. Plasma electrolyte levels may also change after peritoneal dialysis exchanges. For these reasons, studies of ECG measurements in dialysis patients should take into account the method of dialysis, hemodialysis or peritoneal dialysis.

The mean QTc intervals were similar in our controls and HD patients. However, as others have reported, however, QTc dispersion was found to be greater in our patients receiving renal replacement therapy compared to normal controls (15).

The cause of prolonged QT dispersion in ESRD may be due to regional differences of ventricular wall stress, which may be caused by ventricular dilatation and fibrosis (20). In addition, transmembrane electrolyte shifts during hemodialysis result in an increase in QTc dispersion. Left ventricular hypertrophy and hypertension, well known consequences of the ESRD itself, are also factors relating to prolongation of QT dispersion (15).

Risks of concomitant iron supplementation, used to optimize the effect of rHuEpo, includes increased free radical generation from free iron, coronary heart disease and infections. Body iron stores are better assessed by TSAT and serum ferritin than by serum iron levels (21). A progressive increase in TSAT or ferritin during iron therapy without a hematopoietic response is an indication that iron supplementation should be stopped (22). Neither TSAT nor serum ferritin levels should be accepted as a determiner of ventricular arrhythmogenesis and myocardial iron accumulation. Elevated serum ferritin levels were found even in those patients who had never received exogenous iron (23). A variety of methods are available for diagnosing iron overload, the "gold standard" being the assessment of the hepatic iron index in a liver biopsy specimen (22,24).

Although some authors preferred automated measurement of the QT interval using built-in algorithms on their ECG machines, such equipment was unavailable to us. One person (E.D.) performed all QT interval measurements manually with a caliper. In a recent study evaluating the effect of a low calcium dialyzate on QTc dispersion, the manual "tangent method" (the end of the T wave was defined as the point where the tangent to the descending limb of the T wave and the isoelectric line intersected) was used (25). But the authors found that QT intervals thus measured could be falsely short compared to measurements made in the standard fashion with calipers.

We were also careful to perform ECGs at the same time of day in all study participants in order to minimize diurnal influences on QT intervals. Molnar et al. found that the QTc dispersion varied as much as 25% between nighttime (during sleep) and daytime levels (18).

Limitations of the study

The main limitation of this study was the acceptance of HD patients with known coronary artery disease, a well known predisposing factor for QTc dispersion prolongation, into the study. We also failed to test for the presence of other pathology associated with increased QT dispersion, such as left ventricular hypertrophy, pericardial effusion, and segmental wall motion abnormalities. A larger patient population may have resulted in detection of transferrin saturation (p=0.075) as being significantly associated with QTc dispersion.

Conclusion

Transferrin saturation and serum ferritin level, commonly used markers of body iron status, do not correlate with QTc dispersion in patients receiving hemodialysis.

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