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Prolongation of Corrected QT Interval Is a Strong Predictor of Arterial Stiffness in Maintenance Hemodialysis Patients: A Prospective Observational Study

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ABSTRACT

Background: Rate of mortality due to cardiovascular diseases is high in Maintenance Hemodialysis (MHD) patients. Additionally, prolonged QT interval is reportedly associated with high-risk ventricular arrhythmia and sudden death. Vascular calcification may be related to QT dispersion interval in MHD patients because the extensive nature of the calcification process may involve the conducting system and myocardium.

Objectives: This study aimed to evaluate the relationship between QT interval and Pulse Wave Velocity (PWV) as a sign of arterial stiffness associated with atherosclerosis in MHD patients.

Patients and Methods: This prospective, observational study was conducted on 149 eligible MHD patients for 12 months. Patients using drugs known to affect QT interval were excluded. The patients were divided into four groups as follows: normal corrected QT (QTc) interval at the beginning and end of the study (n = 44, 29.5%), normal QTc interval at the beginning but prolonged QTc interval at the end of the study (n = 30, 20.1%), prolonged QTc interval at the beginning but normal QTc interval at the end of the study (n = 24, 16.1%), and prolonged QTc interval at the beginning and end of the study (n = 51, 34.2%). Demographic parameters, laboratory parameters, and PWV were assessed at the beginning and the 12th month of the study. Then, the data were analyzed using ANOVA or Pearson 2 test and $P < 0.05$ was considered to be statistically significant.

Results: The study groups were similar with respect to age and comorbidities, including diabetes mellitus, hypertension, and dyslipidemia. In addition, there were no significant differences among the groups regarding the initial PWV ($P = 0.412$); however, the ending PWV showed significant differences ($P = 0.029$). The results of multivariate analysis showed that PWV was independently associated with change in the maximum QTc (confidence interval: 0.039 – 1.787, $P = 0.031$, $\beta = 0.178$).

Conclusions: The results suggested inclusion of QTc interval prolongation, as a predictor of cardiovascular disease, either alone or in combination with PWV in such high-risk patients.

►*Implication for health policy/practice/research/medical education:*
Chronic dialysis patients have a high risk of death due to cardiovascular events. This study examined the relationship between QT interval and pulse wave velocity as a sign of arterial stiffness. QTc interval prolongation could be a predictor of cardiovascular disease either alone or in combination with pulse wave velocity in such high-risk patients.

1. Background

Chronic hemodialysis patients have a high risk of death due to cardiovascular events. Cardiac disease accounts for approximately 40% of all-cause mortality in Maintenance Hemodialysis (MHD) patients. According to the United States Renal Data System, the single largest specific cause of death is arrhythmic mechanisms or Sudden Cardiac Death (SCD). Ventricular arrhythmias and SCD have

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a higher incidence in MHD patients than in the normal population (1-3).

QT interval is a measure of ventricular electrical recovery after excitation. Cardiac ion channels disturbances, decreased autonomic tone, and myocardial ischemia have been suggested to extend this interval. QT interval prolongation has been reported to be closely associated with Cardiovascular Disease (CVD), electrolyte abnormalities, some commonly used drugs, ventricular arrhythmias, and SCD (4-7).

The etiology of the acquired form of QT interval prolongation has not been clearly defined. Nevertheless, several epidemiological studies have reported a close relationship between QT interval prolongation and clinical/subclinical arterial disease, carotid intima thickness, and sudden death (8-10). SCD is the most common cause of death in patients with End-Stage Renal Disease (ESRD) and is much more common in these patients than in the general population (11, 12). However, there is a limited understanding of the risk factors that place patients with ESRD at a high risk of SCD. QT interval prolongation is also reportedly an independent predictor of mortality in patients with ESRD (13, 14). Many factors, such as electrolyte shifts, increase in serum bicarbonate level, composition of dialysate, and subclinical progressive arterial disease, might underlie the relationship between QT prolongation and the risk of mortality in this population (15-17).

Arterial stiffness is a non-traditional risk factor for CVD and an important contributor to the high rate of cardiovascular mortality associated with MHD (18). Measurement of arterial stiffness is a widely-used noninvasive method to assess Pulse Wave Velocity (PWV) and endothelial dysfunction. Changes in these parameters could be associated with a higher risk of development of CVD (19, 20).

Apart from traditional risk factors (hypertension, diabetes mellitus, and dyslipidemia), uremia-related risk factors are also thought to play an important role in development of CVD. Arterial stiffness is one of these emerging risk factors. It may be hypothesized that vascular calcification is related to QT dispersion interval in patients undergoing hemodialysis because the extensive nature of the calcification process may involve the conducting system and myocardium in this population. Thus, determination of both QT interval and PWV might be helpful to predict life-threatening arrhythmic events and sudden death in MHD patients.

2. Objectives

This study aims to determine whether PWV and corrected QT (QTc) interval are independent or collinear after controlling for all possible confounding factors (diabetes mellitus, hypertension, dyslipidemia, duration of hemodialysis, and age) during a 1-year follow-up of MHD patients at a high risk of SCD.

3. Patients and Methods

3.1. Subjects and Data

This prospective, observational study was conducted on 149 patients undergoing MHD for at least 12 months. Written informed consent was obtained from each subject following a detailed explanation of the study protocol. This study was performed in accordance with the ethical principles stated in the "Declaration of Helsinki" and was approved by Baskent University Institutional Review Board (project No. KA13/181).

Patients were selected among 270 MHD patients according to the following exclusion criteria: 1) hospitalization or acute illness during the follow-up period, 2) malignant diseases or history of tuberculosis, 3) rheumatologic or chronic inflammatory diseases of unknown origin, 4) systemic vasculitis, 5) chronic liver disease, 6) inadequate dialysis ($Kt/V < 1.4$), 7) unstable cardiac disease including heart failure (ejection fraction < 50%) and/or already-known ischemic heart disease (acute myocardial infarction or need for cardiac revascularization) before initiation of the study or during the follow-up period, 8) significant peripheral arterial disease that might affect PWV measurement, 9) atrial fibrillation or intraventricular conduction disturbance (QRS interval > 120 ms), 10) elevated heart rate (> 100 beats/min), 11) use of antiarrhythmic drugs or concomitant treatment with CYP3A4 inhibitors and/or drugs with a direct effect on cardiac depolarization (i.e., erythromycin or ketoconazole), 12) smoking, and 13) recurrent interdialytic hypervolemia.

All patients were undergoing bicarbonated MHD using a low-flux synthetic dialyzer with an average blood flow of 300 to 350 mL/min. Kt/V values were calculated monthly through predialysis and immediate postdialysis blood urea nitrogen levels using a single-compartment model of hemodialysis. The urea kinetics were maintained at $Kt/V > 1.4$.

Data on the patients' demographics, duration of dialysis in years, etiology of chronic kidney disease, and comorbidities were recorded for each patient and compared among the study groups. In addition, levels of the following biochemical parameters were assessed monthly before and after hemodialysis sessions: serum creatinine, albumin, C-Reactive Protein (CRP), calcium, phosphorus, Parathyroid Hormone (PTH), hemoglobin, uric acid, bicarbonate, sodium, and potassium. Besides, the recombinant human erythropoietin (rHuEPO) requirements of the previous 12 months were collected from the patients' charts. The mean adjusted vitamin D doses were also collected retrospectively. The mean values of all parameters were recorded as the final data. The 1- and 12-month values were used for separate statistical analyses.

3.2. Electrocardiographic Evaluation

All patients were evaluated with standard resting 12-lead electrocardiographic (ECG) recordings at the beginning of the study. The end of the T wave was defined as the intersection of the isoelectric line with the tangent to the point of inflection with the descending part of the T wave. If the T wave end-point was slurred or the U wave was prominent, the lead was excluded. Each QT interval was corrected for heart rate with Bazett's formula ($QTc = \text{QT interval duration [ms]} / (60/\text{heart rate})^{1/2}$) (21). A QTc interval of > 450 ms for men and ≥ 460 ms for women was considered to be abnormally prolonged (22). The maximum QT interval was also corrected for the heart rate (QTcmax),

and QTc dispersion (QTdc) was determined as the difference between the maximum and minimum QTc in different leads on the same ECG recording. ΔQTcmax was calculated as (QTcmax2 – QTcmax1) / QTcmax2. It should be noted that all ECG measurements were performed before a mid-week predialysis session.

MHD patients were divided into four groups according to their QTc intervals. Group A patients (n = 44, 29.5%) had a normal QTc interval at both beginning and end of the study. Group B patients (n = 30, 20.1%) had a normal QTc interval at the beginning but a prolonged QTc interval at the end of the study. Group C patients (n = 24, 16.1%) had a prolonged QTc interval at the beginning but a normal QT interval at the end of the study. Finally, Group D patients (n = 51, 34.2%) had a prolonged QTc interval at both beginning and end of the study.

3.3. PWV Measurement

All patients' PWVs were evaluated at the beginning and end of the study. Femoral and carotid artery waveforms were consecutively obtained using a SphygmoCor device (AtCor Medical, West Ryde, Australia) and customized software. Continuous pulse pressure wave signals were recorded with a tonometer (SphygmoCor device with Millar arterial pressure tonometer; AtCor Medical) positioned at both base of the right common carotid artery and over the femoral artery. Distances from the carotid sampling sites to the manubrium sternum and from the manubrium sternum to the femoral artery were measured, as well. The mean transit time between the feet of simultaneously recorded waves was determined from 10 consecutive cardiac cycles. PWV was calculated using the distance between the measurement points and the measured time delay as follows: PWV = D / t, where D and t represented distance in meters and time in seconds, respectively. The methodology was previously described and validated (23). Changes in PWV at the beginning and end of the study were evaluated.

3.4. Statistical Analysis

The Statistical Package for the Social Sciences (SPSS for Windows, ver. 14; Chicago, IL, USA) was used for data analysis. At first, the data were submitted to a frequency distribution analysis by Kolmogorov–Smirnov test. Values displaying normal distribution were expressed as mean ± standard deviation, while those with skewed distribution were expressed as median with interquartile range. Differences between numerical variables were tested using independent samples Student's t-test or Mann–Whitney U test where appropriated. On the other hand, the categorical data were compared by paired samples t-test or Wilcoxon test where appropriated. One-way ANOVA with Tukey's post-hoc test or Kruskal–Wallis test was also used for comparison of more than two groups. Pearson's and Spearman's tests were used according to the distribution characteristics for correlation analysis. Multiple linear regression was performed to identify the variables related to the predictors of ΔQTcmax. A logistic regression model was also applied where ΔQTcmax was the independent variable and independent variables were identified based on the univariate analyses. The significant variables in ANOVA were entered into the model. Variables acting as confounders were also included (i.e., diabetes mellitus, hypertension, dyslipidemia, duration of hemodialysis, age, and biochemical variables). $P < 0.05$ was considered to be statistically significant.

4. Results

Demographic and clinical characteristics of the 149 MHD patients have been summarized in Table 1. Among the patients, 75 (50.3%) had an abnormally prolonged QT interval at the beginning, while 68 (45.6%) had a prolonged QT interval at the end of the study.

The results revealed no statistically significant differences among the four groups regarding laboratory parameters (PTH, serum calcium, serum phosphorus, calcium–phosphorus product, serum albumin, CRP, hemoglobin, sodium, potassium, bicarbonate, and uric acid levels) at either the beginning of the study or the 12-month follow-up. Likewise, no statistically significant differences were found among the four groups concerning the mean adjusted

Table 1. Demographic and Clinical Characteristics of the Four Groups

	Group A, (n = 44)	Group B, (n = 30)	Group C, (n = 24)	Group D, (n = 51)	P value
Age (years)	48.7 ± 17.3	56.1 ± 11.7	52.6 ± 13.0	52.8 ± 17.1	0.249
Duration of HD in years, median (IR)	5 (10.0)	10.5 (7.3)	6 (12.0)	7 (11.0)	0.605
CKD etiology					
DM	9 (20.5)	5 (16.7)	4 (16.7)	9 (17.6)	0.998
HT	6 (13.6)	5 (16.7)	5 (20.8)	9 (17.6)	
GN	6 (13.6)	5 (16.7)	3 (12.5)	6 (11.8)	
PCKD	2 (4.5)	1 (3.3)	1 (4.2)	4 (7.8)	
Unknown	9 (20.5)	6 (20.0)	6 (25.0)	7 (13.7)	
Others	12 (27.3)	8 (26.7)	5 (20.8)	16 (31.4)	
Comorbidities					
DM	11 (25.0)	7 (23.3)	8 (33.3)	10 (19.6)	0.664
HT	18 (40.9)	13 (43.3)	8 (33.3)	22 (43.1)	0.954
Dyslipidemia	5 (11.4)	4 (13.3)	3 (12.5)	7 (13.7)	0.759
Female	17 (38.6)	11 (36.7)	11 (45.8)	18 (35.3)	0.848

Abbreviations: IR, interquartile range; CKD, chronic kidney disease; DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HT, hypertension; PCKD, polycystic kidney disease

Data are presented as mean ± standard deviation or n (%) unless otherwise indicated.

vitamin D dose and mean rHuEPO dose.

PWV changes were evaluated according to the initial PWV (PWV-1, mean: 7.82 ± 2.81 m/s) and ending PWV (PWV-2, (mean: 7.81 ± 3.03 m/s). The results of ANOVA indicated no significant differences among the four QTc groups regarding their PWV-1 (P = 0.412). However, the four groups were significantly different with respect to PWV-2 (P = 0.029) (Table 2). A subgroup analysis of the differences among the four groups concerning PWV changes was also performed. According to the results, only group D patients had significantly longer PWV measures compared to those in group A (P = 0.036, not shown in the table).

The four groups were also compared with regard to changes in their QTcmax and QTdc values at the beginning and end of the 1-year follow-up. The results revealed statistically significant changes, which have been summarized in Table 3. Accordingly, QTdc values were positively correlated to QTcmax values at both beginning and end of the study (r = 0.491, P = 0.001 and r = 0.208, P = 0.01, respectively). Additionally, ΔQTcmax was positively correlated to PWV-2 (r = 0.175, P = 0.033). Moreover, the results of multiple linear regression model showed that PWV was the only independent predictor of ΔQTc duration (95% confidence interval: 0.039 – 0.787, P = 0.031) (Table 4).

5. Discussion

Previous studies have reported that QTc interval was significantly longer in dialysis patients than in healthy subjects (24). A prolonged QTc interval has been proven to be associated with electrical instability of the myocardium, leading to adverse cardiovascular outcomes including ventricular fibrillation and SCD (25). Several studies have also demonstrated the acute effects of dialysis on QTc interval (17, 26). In the present study, no dramatic changes were observed in plasma electrolyte concentrations before and after hemodialysis sessions. This indicates that in addition to plasma electrolyte concentrations, non-traditional cardiovascular risk factors associated with uremic condition may play a role in determining electrocardiographic alterations.

Hemodialysis is known to prolong the QTc interval, but its relationship with arterial stiffness and subclinical

Table 2. Baseline and 12-Month Pulse Wave Velocity Measurements in All Groups

	Group A, (n=44)	Group B, (n=30)	Group C, (n=24)	Group D, (n=51)	P value
PWV-1 (m/s)	7.4 ± 2.4	7.6 ± 3.2	7.8 ± 2.9	8.3 ± 2.8	0.412*
PWV-2 (m/s)	6.9 ± 2.3	8.2 ± 3.6	7.2 ± 1.5	8.6 ± 3.4	0.029

Abbreviations: PWV, pulse wave velocity

Data are presented as mean ± standard deviation.

* P value for comparisons among all groups.

Table 3. Baseline and 12-Month Corrected QT Maximum and Dispersion in the Four Groups

	Group A, (n = 44)	Group B, (n = 30)	Group C, (n = 24)	Group D, (n = 51)	P value*
QTcmax, 1 month	429.0 ± 20.2	430.1 ± 18.7	476.0 ± 19.2	481.6 ± 22.6	0.001
QTcmax, 12 months	430.4 ± 14.6	471.3 ± 15.5	436.9 ± 9.2	490.1 ± 28.2	0.001
QTdc, 1 month	52.1 ± 14.1	48.5 ± 13.3	63.6 ± 21.3	68.8 ± 20.4	0.001
QTdc, 12 months	43.6 (19.8)	53.3 (27.0)	48.7 (10.6)	63.6 (31.2)	0.001

Data are presented as mean ± standard deviation or median (interquartile range). QTcmax, corrected maximum QT interval; QTdc, corrected QT dispersion

* P values for comparisons among all groups.

Table 4. The Results of Multiple Linear Regression Models for ΔQTc Maximum

Variables	B (SE)	P value
Age at recruitment	0.03 (0.04)	0.537
Hemodialytic duration	0.08 (0.1)	0.428
Diabetes mellitus	–0.7 (1.7)	0.682
Hypertension	–1.6 (1.3)	0.229
Dyslipidemia	–0.9 (1.9)	0.657
Mean hemoglobin (g/dL)	0.2 (0.2)	0.418
Mean albumin (g/dL)	–0.4 (2.3)	0.874
Mean C-reactive protein (mg/L)	0.05 (0.05)	0.339
Mean parathyroid hormone (pg/mL)	0.002 (0.002)	0.257
Mean phosphorus (mg/dL)	0.5 (0.6)	0.415
Mean calcium (mg/dL)	–1.1 (1.1)	0.304
Mean potassium before session (mmol/L)	–0.5 (0.8)	0.533
Mean potassium after session (mmol/L)	0.8 (1.2)	0.486
Mean sodium (mmol/L)	–0.01 (0.04)	0.708
Mean uric acid (mg/dL)	0.2 (0.6)	0.744
Pulse wave velocity-1 (m/s)	–0.3 (0.3)	0.296
Pulse wave velocity-2 (m/s)	0.4 (0.2)	0.031

arterial disease was a new finding. Several recent studies have confirmed the high prevalence of QTc prolongation in patients with ESRD (30 - 45%) (11, 27). The current study results also revealed prolonged QTc intervals in 67% of the MHD patients. The high incidence of prolonged QTc interval in this study might be attributed to the longer duration of dialysis in our patients than in other studies involving dialysis patients. Many uremia-related factors might have also contributed to ECG abnormalities.

Few cross-sectional studies on the general population have suggested a positive association between QT interval prolongation and arterial stiffness, such as carotid intima media thickness (28). PWV is an established marker of arterial stiffness (29). To the best of our knowledge, our study is the first to examine the relationship between PWV and heart rate-corrected QT interval. The results indicated that not only the single measure of the QTc interval, but also changes in QTc duration during a 1-year period had a significant relationship with PWV. Additionally, both the initial and follow-up prolongation of the QTc were closely related to PWV in the MHD patients. This association remained even after controlling for traditional cardiovascular risk factors, suggesting an independent relationship between arterial stiffness and QT interval prolongation. These data supported the idea that subclinical arterial disease was closely associated with QT interval prolongation in patients with and without ESRD (3). Furthermore, our PWV measurements revealed that not only patients with known QTc prolongation, but also those who acquired QTc prolongation during the follow-up period had significantly higher PWV values. The results demonstrated that progression of arterial stiffness might predict QTc interval prolongation in the MHD patients. However, the exact mechanism underlying the association between arterial stiffness and the acquired form of QTc interval prolongation has not yet been clearly defined in the general and dialysis populations. Subclinical arterial disease and the subsequent arterial stiffness might increase the ventricular load and, as a consequence, might promote myocardial and electrophysiological remodeling, resulting in QT interval prolongation (30). Another possible mechanism is that microvascular atherosclerosis in the coronary artery, which is strongly related to systemic arterial disease, might lead to subendocardial ischemia and thus extend the QT interval (31). Uremic state and presence of uremic cardiomyopathy might also be strong contributing factors.

The main drawback of our study might be its small patient population. Our patients with ESRD did not undergo coronary angiography, which is the gold standard diagnostic tool for coronary artery disease. Although the results demonstrated a strong correlation between QTc interval prolongation and arterial stiffness, no evidence was found regarding the impact of prolonged QT interval on cardiovascular mortality and SCD in the dialysis patients. A longer study duration might have been more appropriate for the use of PWV as a predictor and would provide more data on morbidity, mortality, and SCD in our study population. A 24-hour ECG rhythm Holter evaluation could also be planned to observe the impact of prolonged QT interval on arrhythmia. Another drawback of our study might be the absence of data regarding the left ventricular mass. Thus, a randomized controlled trial including ECG data is recommended to be performed in a larger patient population to evaluate the association between QT prolongation and left ventricular mass. Despite these limitations, our data revealed a close association between arterial stiffness and QTc prolongation in the MHD patients.

In conclusion, the current study findings showed a close association between arterial stiffness and QTc interval prolongation in the MHD patients. PWV measurement combined with yearly ECG evaluation and analysis of changes in QTc interval could be used as a noninvasive and easy technique for detection of cardiovascular risk in MHD patients. Thus, QTc interval prolongation is suggested to be included as a predictor of CVD either alone or in combination with PWV in such high-risk patients. Yet, future longitudinal studies are necessary to clarify the causal relationship between arterial stiffness and QT interval prolongation.

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Authors' Contribution

Zeynep Bal and Ugur Bal drafted the article; Emre Tutal, Siren Sezer, and Mehtap Erkmen Uyar performed data analysis and interpretation; Siren Sezer provided intellectual content of critical importance to the work; Zeynep Bal was primary responsible for the final content.

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