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# A COMPARATIVE STUDY TO EVALUATE THE EFFECT OF HEMODIALYSIS ON MAXIMUM CORRECTED QT INTERVAL (QTCMAX) AND QT DISPERSION IN CHRONIC KIDNEY DISEASE

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## ABSTRACT
Sudden cardiac death is common in patients on hemodialysis, and may occur in the immediate postdialysis period, when ventricular premature complexes are common. Elevated QT dispersion is associated with increased risk of ventricular arrhythmias following myocardial infarction, but has not previously been assessed in patients with chronic renal failure. We studied electrocardiograms recorded in 50 patients before and after a single hemodialysis session between February 2018 and July 2018. QT dispersion was prolonged in patients before hemodialysis (63.1 6 20.6 ms) and significantly increased after hemodialysis to levels comparable to those seen following myocardial infarction (76.6 6 27.0 ms; *P*, 0.01). Because QT dispersion reflects nonhomogeneous recovery of ventricular excitability, hemodialysis patients may be at significantly greater risk of reentrant arrhythmias and sudden death in the postdialysis period.

**KEYWORDS:** Hemodialysis, QT interval, QT dispersion, chronic renal failure.

## INTRODUCTION
**C**ardiovascular diseases represent the main causes of death (especially sudden cardiac death) in patients affected by renal failure and chronic hemodialysis.[1,2] The reasons for great incidences of arrhythmia and death are complex and multifactorial.[3] Dialytic treatment per se can be considered as an arrhythmogenic stimulus, moreover, uremic patients are characterized by a pro-arrhythmic substrate because of the high prevalence of ischaemic heart disease, left ventricular hypertrophy and autonomic neuropathy, myocardial dysfunction, changes in electrolyte concentration like calcium and potassium.[1,4-8] Among the noninvasive techniques which can be useful for predicting the patients at risk for sudden death is the measurement of QT interval changes with 12-lead surface electrocardiogram.[9]

QT dispersion (QTd) defined as maximum QT interval minus minimum QT interval for a given set of electrocardiogram lead, was proposed as an approximation for repolarization abnormalities and measured for regional heterogeneity of myocardial refractoriness.[10,11] Prognostic value of QTd was evaluated in patients with end stage renal disease patients requiring hemodialysis and in patients with diabetes mellitus.[12] The purpose of this study was to assess the effect of hemodialysis (HD) on QT and corrected QT (QTc) intervals and dispersion.

## MATERIALS AND METHODS
This was a Prospective study in the dialysis unit of Department of nephrology. The study was approved by the institutional human ethics committee. Patients were required to provide written informed consent prior to entering the study. After taking written informed consent, fifty patients with chronic renal failure on three-times-a-week hospital hemodialysis were randomly selected. A detailed history into duration and etiology of CKD and drug intake was taken and detailed examination was done in each case. Demographic characteristics including age, sex, weight, height, body mass index, duration on chronic intermittent hemodialysis, were recorded in each patient. Blood pressure was recorded before and after hemodialysis. Forty-seven patients had ECG that were suitable for inclusion in the study (two had atrial fibrillation and one had left bundle branch block). The underlying causes of chronic renal failure (when known) were: chronic glomerulonephritis (*n* 12), diabetic nephropathy (*n* 11), ureteric reflux/obstructive nephropathy (*n* 9), polycystic kidney disease (*n* 2), renovascular disease (*n* 2), myeloma (*n* 2), hypertension (*n* 1), analgesic nephropathy (*n* 1), and interstitial nephritis (*n* 1). The

median (range) time on renal replacement therapy was 18 (1 to 203) months. Ischemic heart disease (previous myocardial infarction, angina, or coronary artery bypass grafting) was present in nine patients, and hypertension before onset of renal replacement therapy was present in 32 patients. The exclusion criteria included patients with known atrial fibrillation, supraventricular or ventricular ectopics, paroxysmal supraventricular tachycardia, and left bundle branch block; patients on antiarrhythmic drugs known to prolong the QT interval (e.g class I or III antiarrhythmic drugs, macrolides, fluoroquinolones, quinidine, halofantrine, ketoconazole, itraconazole, tricyclic antidepressants, antipsychotics).

Routine biochemistry levels, including magnesium and calcium corrected for serum albumin, were measured pre- and postdialysis, at the time of the ECG. The volume of fluid removed at ultrafiltration was recorded (2.94 6 0.95 L [mean 6 SD]), and the ultrafiltration rate was calculated (0.64 6 0.20 L/h).

***Electrocardiographs***

Twelve-lead electrocardiographs were performed at 10 mm/mv and 50 mm/s using a Hewlett-Packard Pagewriter 100, before and immediately after a single hemodialysis session. ECG were performed with the patient lying at 45° using adhesive electrodes. ECG were coded and analyzed blindly for QT intervals by one observer using a digitizer. The QT interval was measured from the onset of the QRS complex to the end of the T wave. When T waves were inverted, the end was taken at the point where the trace returned to the T-P baseline, and when U waves were present, the end of the T wave was taken as the nadir between the T and U waves. If the end of the T wave was not clear in a particular lead then it was excluded from analysis; for any particular ECG, no more than three leads were excluded. Three successive QT interval measurements were performed in each of the 12 leads, and the mean value was calculated. The maximum QT interval was corrected for heart rate (QTcmax) using Bazett's formula QTc 5 QT/=(RR) (11). Intraobserver variability, assessed by re-variation). We also measured two ECG indices of left ventricular hypertrophy (LVH), the Cornell voltage (RaVL plus SV3) (12), and the Sokolow Lyon voltage (SV1 plus RV5 or V6) (13), and calculated cardiac axis by measuring the area under the QRS in two limb leads and plotting these as vectors on a triaxial reference system (14).

***Statistical Analyses***

Statistical analyses were performed using the Statistical Package for the Social Sciences version 6 (SPSS 6) for Windows. Results were tested for normality and expressed as mean 6 SD, or median 6 range as appropriate. Comparisons were made using *t* test and Mann-Whitney test (electrolyte values). Univariate correlation coefficients were examined to assess the effects of electrolyte, cardiac axis, and BP changes, and ultrafiltration (UF) volume, on QT dispersion. A multiple regression analysis was also performed with QT dispersion postdialysis as the dependent variable (positive number), and entering UF volume, diastolic BP postdialysis, cardiac axis postdialysis, age, and bicarbonate postdialysis into the model.

**RESULTS**

Fifty patients with chronic renal failure on three-times-a-week hospital hemodialysis were randomly selected. Forty-seven patients had ECG that were suitable for inclusion in the study (two had atrial fibrillation and one had left bundle branch block) with a mean age of 53± 17 years The underlying causes of chronic renal failure (when known) were: chronic glomerulonephritis (*n* 12), diabetic nephropathy (*n* 11), ureteric reflux/obstructive nephropathy (*n* 9), polycystic kidney disease (*n* 2), renovascular disease (*n* 2), myeloma (*n* 2), hypertension (*n* 1), analgesic nephropathy (*n* 1), and interstitial nephritis (*n* 1). The median (range) time on renal replacement therapy was 18 (1 to 203) months. Ischemic heart disease (previous myocardial infarction, angina, or coronary artery bypass grafting) was present in nine patients, and hypertension before onset of renal replacement therapy was present in 32 patients.

Maximum corrected QT interval (QTcmax) and QT dispersion (corrected and uncorrected for heart rate) were both significantly higher in patients (predialysis) and rose significantly postdialysis (Table 2). Both indices of LVH were elevated in dialysis patients (strain detected in nine), confirming the known high prevalence of LVH in this group. In addition, mean cardiac axis was more to the left, and both the Sokolow and Cornell voltages rose significantly postdialysis. The changes in QT dispersion and QTcmax across dialysis remained significant in the 38 patients without ischemic heart disease, suggesting that the dialysis process itself influences these parameters (Table 3). Electrolyte changes associated with hemodialysis are depicted in Table 4. Multiple regression analysis was performed in those patients without ischemic heart disease to assess the potential influence of various factors on the QT dispersion postdialysis; the following independent factors were entered into the model: ultrafiltration volume, age, axis postdialysis, diastolic BP postdialysis, and serum bicarbonate postdialysis. Results are depicted in Table 5, and show that only bicarbonate appeared to be an independent predictor of QT dispersion postdialysis.

**Table 1: Baseline characteristics.**

| CHARACTERISTICS | PRE DIALYSIS | POST DIALYSIS | P VALUE |
|---|---|---|---|
| AGE | 53± 17 | | |
| MALE/ NUMBER | 32/47 | | |
| BMI | 25.1± 3.5 | | |
| BLOOD UREA (mmol/l) | 20.3± 4.4 | 6.4± 1.9 | <0.001 |
| SERUM CREATININE (mmol/l) | 799± 201 | 317± 83 | <0.001 |
| SBP (mm Hg) | 155.8± 30.4 | 135.5 ±30.2 | <0.001 |
| DBP (mm Hg) | 82.7 ±14.6 | 72.9 ±15.0 | <0.001 |
| HEART RATE | 83.5± 14.23 | 84.8± 14.9 | NS |

a. Results are given as mean 6 SD.
b Corresponds to a two-tailed *t* test comparing control subjects with patients predialysis.
c Corresponds to a two-tailed paired *t* test comparing patients pre- and postdialysis.

**Table 2: ECG results for patients pre- and post dialysis.**

| PARAMETERS | PRE DIALYSIS | POST DIALYSIS | P VALUE |
|---|---|---|---|
| QTcmax (ms) | 480.1 ±35.4 | 496.9 ±42.9 | <0.001 |
| QTdisp (ms) | 63.1 ±20.6 | 76.6± 27.0 | <0.01 |
| QTcdisp (ms) | 75.9± 25.3 | 91 ±29.7 | <0.01 |
| Axis (°) | 14.3± 30.4 | 20.8± 33.8 | <0.05 |
| Sokolow (mV) | 29.76± 9.27 | 34.03± 11.57 | <0.001 |
| Cornell (mV) | 22.69± 9.57 | 24.67± 10.28 | <0.01 |

a Results are given as mean 6 SD. ECG, electrocardiogram; QTcmax, maximum QT interval corrected using Bazett's formula; QTdisp, QT dispersion; QTcdisp, Maximum 2 Minimum QTc interval.

**Table 3: ECG results for 38 patients with no history of ischemic heart disease.**

| PARAMETERS | PRE DIALYSIS | POST DIALYSIS | P VALUE |
|---|---|---|---|
| QTcmax (ms) | 474.4± 32.6 | 489.7± 39.7 | <0.01 |
| QTcdisp (ms | 60.7 ±19.6 | 72.4 ±26.3 | <0.01 |
| QTcdisp (ms) | 74.1± 26.0 | 86.7± 29.6 | 0.01 |
| Axis (°) | 20.7± 28.1 | 28.7 ±29.9 | 0.01 |
| Sokolow (mV) | 30.1± 8.7 | 34.2 ±11.3 | 0.001 |
| Cornell (mV) | 22.3 ±9.8 | 24.1± 10.6 | 0.059 |

a Results are given as mean 6 SD. Comparison is by paired *t* test. Abbreviations as in Table 2.

**Table 4: Electrolyte results pre- and postdialysis.**

| | PRE DIALYSIS | POST DIALYSIS | P VALUE |
|---|---|---|---|
| POTASSIUM (mmol/l) | 4.7 (3.1-6.2) | 3.1 (2.4- 4.2) | <0.001 |
| MAGNESIUM (mmol/l) | 0.69 (0.5-1.2) | 0.55 ( 0.3 - 0.7) | <0.001 |
| CALCIUM (mmol/l) | 2.43 ( 2-2.9) | 2.34 ( 2.1 – 2.9) | <0.01 |
| BICARBONATE (mmol/l) | 21 ( 15-27) | 25 ( 21 – 29) | <0.001 |

a Results are given as median (range).

**Table 5: Multiple regression analysis with QTdispersion postdialysis as dependent variable in patients with no ischemic heart disease.**

| VARIABLE | B | STD ERROR OF ESTIMATE | BETA | SIGNIFICANCE |
|---|---|---|---|---|
| BIC POST | 4.26 | 1.77 | 0.36 | 0.022 |
| AGE | 0.14 | 0.22 | 0.09 | 0.539 |
| DBP POST | 0.50 | 0.27 | 0.29 | 0.262 |
| AXIS POST | -0.06 | 0.14 | -0.07 | 0.682 |
| UF | -6.18 | 3.96 | -0.23 | 0.128 |

Multiple *r* 5 0.59, *r*2 5 0.35, standard error of estimate 22.81, *P* 5 0.014. Beta, standardized coefficient of regression; B, regression coefficient; BIC, bicarbonate; DBP, diastolic BP; UF, ultrafiltration.

## DISCUSSION

This study demonstrates that QTc dispersion is higher in hemodialysis patients, and rises post dialysis to levels comparable to those seen acutely following myocardial infarction,[10] when patients are at greatly increased risk of potentially fatal ventricular arrhythmias. The results are also highly significant before correction using Bazett's formula, a method used in standard practice, but

recently criticized as introducing unnecessary error into measurement and interpretation of QT interval values.[13] Because QT dispersion reflects nonhomogeneous recovery of ventricular excitability, the results suggest that dialysis patients may be at higher risk of reentrant arrhythmias, and that this risk rises in the immediate post dialysis period. The higher QT dispersion in dialysis patients may reflect the known higher prevalence of echocardiographically determined LVH in this group, a finding confirmed by the increased Cornell and Sokolow voltages in the present study. However, the mechanisms responsible for the increased QT dispersion post dialysis are unclear. We accept that the measurement of QT dispersion by a manual observer is prone to error, and in this study the coefficient of variation was 15%. We have attempted to minimize any error by using a single blinded observer for all ECG pre and post dialysis, by measuring the QT interval in three complexes from each lead and using the average of these measurements, and by discarding leads where the end of the T wave was unclear. The error with automated methods may be similar if not greater, and a standardization of the methodology is required before QT dispersion can be widely adopted as a routine clinical tool.

In conclusion, this study showed that QTcmax and QT dispersion, markers of risk for arrhythmias and sudden death, are elevated in hemodialysis patients, and rise postdialysis. The mechanisms responsible are unclear but may reflect myocardial ischemia in those patients with known ischemic heart disease (mediated through a fall in diastolic BP during dialysis), or changes in acid-base status in patients without ischemic heart disease. Additional larger studies are required to assess the importance of QT dispersion on cardiovascular outcome in chronic renal failure, and QT dispersion may prove a novel target for intervention studies to reduce sudden death in this high-risk population.

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