

## Original Paper

# QT Interval and QT Dispersion in Patients Undergoing Hemodialysis: Revisiting the Old Theory

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## Key Words

QT interval · QT dispersion · Hemodialysis

## Abstract

**Aims:** We sought to explore the response of the corrected QT (QTc) interval duration and QT dispersion (QTD) to hemodialysis. **Methods:** We enrolled 50 patients with end-stage renal disease undergoing regular hemodialysis. Blood samples were drawn for measurement of serum electrolytes, and a 12-lead ECG was performed to measure the QTc interval duration and QTD, immediately before and just after dialysis sessions. **Results:** The mean age of the cohort was  $42.8 \pm 12.2$  years (58% males). Both the QTc duration and QTD showed marked variability after hemodialysis. A significant correlation was found between the decrease of both serum potassium and magnesium levels after dialysis and the post-dialysis QTc interval duration, with Pearson's correlation coefficients  $r = -0.43$  and  $r = -0.34$ ,  $p = 0.002$  and  $p = 0.01$ , respectively. Patients with a post-dialysis increase of QTc interval duration had a significantly higher percentage of reduction of serum potassium ( $p = 0.029$ ), whereas patients with a post-dialysis increase of QTD had a significantly higher percentage of reduction of serum magnesium ( $p = 0.03$ ). **Conclusion:** Our findings suggest a highly variable response of the QTc interval duration and QTD to hemodialysis. The post-dialysis QTc interval duration inversely correlated with the decrease of both serum potassium and magnesium levels after dialysis.

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## Introduction

Despite the recent advances in hemodialysis technology, mortality is still high among dialysis patients. Cardiovascular mortality is estimated to be 10-fold that of the general population, and it usually occurs suddenly [1–3]. The mechanism responsible for the augmented risk of sudden death in dialysis patients remains unclear; yet, 24-hour Holter monitoring unveiled a high prevalence of ventricular arrhythmias during and immediately following dialysis [1, 4].

There is considerable evidence that the QT interval is closely related to ventricular action potential and is a good non-invasive measure of the repolarization process. Several reports indicate that regional differences in static QT interval measurement (QT dispersion) from 12-lead surface electrocardiogram (ECG) may provide an indirect measure of the underlying non-homogeneity of ventricular repolarization [5]. QT dispersion (QTD) is defined as the difference between the longest and the shortest QT intervals on surface ECG [6]. An increase in QTD is reported to predict the occurrence of life-threatening ventricular tachyarrhythmias and sudden cardiac death in patients with ischemic heart disease [7].

In dialysis patients, both prolongation of the QT interval [8–10] and increase of the QTD [11–13] have been reported during hemodialysis sessions. These alterations of ventricular repolarization might provide a potential substrate for lethal ventricular arrhythmias in this fragile patient category. It is well known, as well, that both hypokalemia and hypomagnesemia can increase the action potential duration and prolong the QT interval. In a cross-sectional study design, we sought to explore the response of the corrected QT (QTc) interval duration and QTD to hemodialysis and evaluate the effect of serum electrolyte changes during hemodialysis on these parameters in patients with end-stage renal disease.

## Materials and Methods

### *Patient Selection and Study Design*

We included 50 clinically stable patients with end-stage renal disease undergoing chronic regular hemodialysis in our dialysis unit; patients were enrolled during March and April 2010. The causes of end-stage renal disease included chronic glomerulonephritis in 13 (26%) patients, hypertensive nephrosclerosis in 9 (18%), obstructive uropathy in 5 (10%), and idiopathic in 6 (12%); 17 (34%) patients had other causes. All patients were dry-weight stable for at least 3 months and had achieved a normotensive edema-free state. All patients were given intravenous erythropoietin 3 times a week (mean dosage  $23 \pm 7$  IU/kg). We excluded patients with known ischemic heart disease, previously diagnosed congenital long QT syndrome, atrial fibrillation, paced rhythm or bundle branch block, known organic heart disease (valvular or hypertensive heart disease, or cardiomyopathy), advanced liver disease, and patients receiving medications known to prolong the QT interval (for example quinine and amiodarone). Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol, and the study protocol was reviewed and approved by our local Institutional Human Research Committee which conforms to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2002.

### *Doppler Echocardiography*

Doppler echocardiography was performed using a General Electric Vivid 7 Pro cardiac ultrasound machine (General Electric, Horten, Norway). A 2.5-MHz phased array probe was used to obtain standard 2-D, M-mode and Doppler images. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Left ventricular

dimensions were evaluated from 2-D-derived M-mode measurements. Biplane left ventricular ejection fraction was estimated from the 2- and 4-chamber views using the modified Simpson's method. Assessment of valve morphology and function as well as regional wall motion abnormalities were performed in the standard way.

#### *Dialysis Regimen*

Dialysis was performed for 3.5–4 h per session, with blood flow 300 ml/min, dialysis membrane AN69, and mean weight loss set at 2.5 kg. All patients were treated with a dialysis regimen of bicarbonate dialysis set at the following electrolyte composition in the bath: Na 138 mEq/l, K 2 mEq/l, Ca 3 mEq/l, Mg 1 mEq/l, Cl 111 mEq/l, acetate 3 mEq/l, and bicarbonate 33 mEq/l. During hemodialysis, no drug therapy was allowed, except isotonic saline infusion and sodium heparin. All dialysis sessions were conducted using an Integra machine (Hospal, Bologna, Italy).

#### *Laboratory Analysis*

A 5-ml venous blood sample was drawn by phlebotomy immediately before and just after dialysis sessions, collected in a sterile tube, immediately put on ice, centrifuged on site within 90 min, and frozen on dry ice. Blood samples were shipped within 24 h to our central laboratory, where they were stored at  $-80^{\circ}\text{C}$  until analyzed. Samples were assessed for serum sodium, potassium, calcium, and magnesium ions. All laboratory analyses were performed using routine automated methods.

#### *Electrocardiographic Assessment*

All enrolled patients underwent a resting high-quality 12-lead ECG recording, which was subsequently evaluated by an expert electrophysiologist blinded to both clinical and lab data. QT interval was measured using the manual technique, as the time in milliseconds between the first deflection of the QRS complex and the point of return of the T wave to the isoelectric line. Measurements were obtained in 3 consecutive complexes in each lead, and the mean value was used. The leads in which the end of the T wave could not be clearly identified were excluded from analysis [14]. In leads with a U wave, the nadir between the T and U waves was considered as the end of the T wave. We recorded the maximal and minimal QT intervals, and calculated the QTD as the difference between the two intervals, which was individually recorded for each patient [15]. We then calculated the QTc interval from the Bazett's formula as follows:  $\text{QTc interval} = \text{QT interval} / \sqrt{\text{RR}}$  [16]. Finally, the QTc dispersion (QTcD) was calculated as the difference between the maximal and minimal QTc intervals. These measurements were estimated 10 min before and 10 min following the dialysis session. The mean values of QT and QTc intervals as well as QTD and QTcD were calculated for the study group, separately, before and after dialysis.

#### *Statistical Analysis*

All continuous variables were presented as means  $\pm$  SD if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Paired t test was used to compare QT intervals, QTD values, and serum electrolytes before and after dialysis within the study group. Pearson's correlation coefficient test was performed to study the correlation between the QT intervals and QTD values, on the one hand, and the change of serum electrolytes following dialysis, on the other hand. All tests were two-sided, and a probability value of  $p < 0.05$  was considered statistically significant. Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, Ill., USA).

**Table 1.** Mean serum electrolyte values before and after hemodialysis in the study group

	Before hemodialysis	After hemodialysis	p
Serum sodium, mEq/l	134.4 ± 2.7	132.7 ± 3.3	<0.01
Serum potassium, mEq/l	5.04 ± 0.85	3.8 ± 0.5	<0.001
Serum calcium, mg/dl	8.05 ± 0.84	9.1 ± 0.7	<0.001
Serum magnesium, mg/dl	2.7 ± 0.35	2.4 ± 0.22	<0.001

All variables are presented as means ± SD.

**Table 2.** Mean values of QTc interval duration and QTD before and after hemodialysis in the study group

	Before hemodialysis	After hemodialysis	p
QT interval, ms	423 ± 43	409 ± 39	<0.001
QTc interval, ms	488 ± 33	488 ± 31	>0.05
QTD, ms	55 ± 23	56 ± 26	>0.05
QTcD, ms	66 ± 24	70 ± 26	>0.05

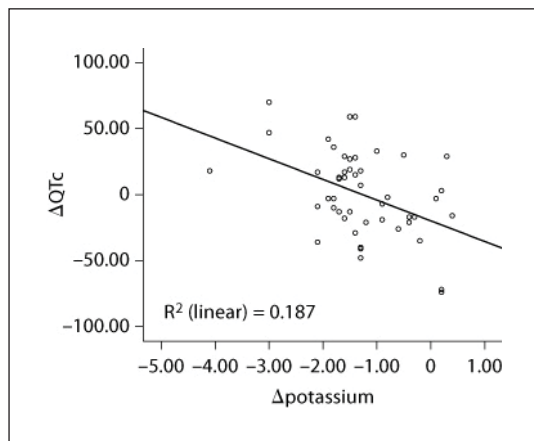
All variables are presented as means ± SD. QTc = Corrected QT; QTcD = corrected QT dispersion; QTD = QT dispersion.

## Results

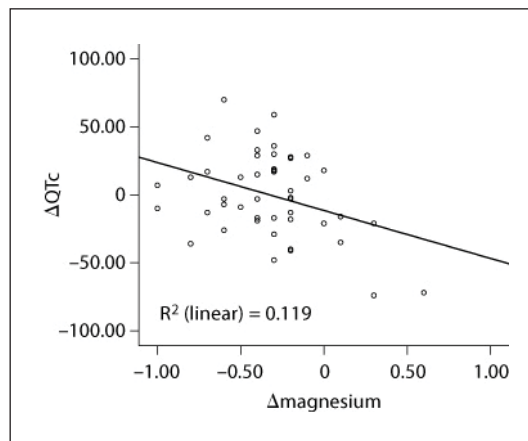
A total of 50 patients with end-stage renal disease on regular hemodialysis were enrolled in the current study. The mean age of the study group was 42.8 ± 12.2 years, 29 (58%) patients being males. Patients were undergoing hemodialysis 3 times a week (3.5–4 h per session); the mean duration of being dependent on dialysis was 6.4 ± 2.7 years (range 2–10 years). Six (12%) patients were diabetic and 33 (66%) were hypertensive. The mean systolic blood pressure was 131 ± 28 mm Hg, whereas the mean diastolic blood pressure was 81 ± 16 mm Hg. Diastolic and mean arterial blood pressures, body weight, and total ultrafiltration were in line with our dialysis prescription in all sessions. The mean values of serum electrolytes before and after dialysis are shown in table 1. The mean QT interval duration and QTD values, before and after dialysis, are shown in table 2.

Both the QTc interval duration and QTD showed marked variability after hemodialysis. Following hemodialysis sessions, the QTc interval duration increased in 23 (46%) patients and decreased in 27 (54%); QTD increased in 20 (40%) patients, decreased in 21 (42%), and remained almost unchanged in the rest. A QTc interval duration of >440 ms was found in 45 (90%) patients before dialysis, whereas after dialysis, it was found in 47 (94%) patients. A QTD of >65 ms was found in 10 (20%) patients before dialysis, whereas after dialysis, it was found in 17 (34%) patients.

A significant correlation was found between the decrease of both serum potassium and magnesium levels after dialysis and the post-dialysis QTc interval duration, with Pearson's correlation coefficients  $r = -0.43$  and  $r = -0.34$ ,  $p = 0.002$  and  $p = 0.01$ , respectively (fig. 1, 2). However, no significant correlation was found between the decrease of either serum sodium or calcium after dialysis and the post-dialysis QTc interval duration ( $p > 0.05$  for both). Similarly, no significant correlation was found between the decrease of any of the serum electrolytes after dialysis and the post-dialysis QTD ( $p > 0.05$  for all).



**Fig. 1.** Scattered diagram of QTc interval values with changes of serum potassium following hemodialysis.



**Fig. 2.** Scattered diagram of QTc interval values with changes of serum magnesium following hemodialysis.

Patients with a post-dialysis increase of QTc interval duration had a significantly higher percentage of reduction of serum potassium as compared to those with a post-dialysis decrease of QTc interval duration ( $28.3 \pm 14$  vs.  $19.1 \pm 14.6\%$ , respectively;  $p = 0.029$ ). Similarly, patients with a post-dialysis increase of QTD had a significantly higher percentage of reduction of serum magnesium as compared to those with no such increase of QTD ( $15.4 \pm 8.2$  vs.  $7.8 \pm 13.1\%$ , respectively;  $p = 0.03$ ).

## Discussion

### Major Findings

The current study demonstrated a marked variability of both the QTc interval duration and QTD in response to hemodialysis. Additionally, the post-dialysis QTc interval duration significantly correlated with the decrease of both serum potassium and magnesium levels after dialysis. Moreover, the percentage of reduction of serum potassium was significantly higher in patients with a post-dialysis increase of QTc interval duration as compared to those with a post-dialysis decrease of this value. Similarly, the percentage of reduction of serum magnesium was significantly higher in patients with a post-dialysis increase of QTD as compared to those with no post-dialysis increase of this value.

### Response of the QTc Interval Duration

Accumulating evidence has been controversial concerning the impact of hemodialysis on the ECG surrogates of ventricular repolarization in patients with end-stage renal disease. Whereas it has long been believed that a dialysis-induced prolongation of the QTc interval duration – and increase of the QTD – was responsible for lethal ventricular arrhythmias during and immediately following hemodialysis, some emerging evidence suggests a decrease – rather than increase – of the QT and/or QTc interval after dialysis [17–19]. Patients with end-stage renal disease are a heterogeneous population in which a complex interplay of many factors determines the response of the QTc interval to hemodialysis. Furthermore, the regimen employed in hemodialysis may also play a role in depicting the ‘final scene’ of ventricular repolarization. In this regard, one comparative study reported that bicarbonate di-

alysis reduces the QT and QTc intervals duration more than acetate-free biofiltration [17]. Since nitric oxide is produced more with the former dialysis regimen as compared with the latter [20], the authors suggested a possible role of nitric oxide in shortening the post-dialysis QT and QTc intervals duration in that study. Nitric oxide excess can depress cardiomyocytes and inhibit vascular smooth muscle cells; these effects were more profound with bicarbonate dialysis [17]. The inverse correlation between nitric oxide and QT interval duration was further demonstrated in the literature [21]. In addition, the electrical remodeling effect of uremic cardiomyopathy and the alterations of ion influx/efflux between the intra- and extracellular compartments might further complicate the picture [22, 23]. Moreover, changes in the rennin-angiotensin system may be implicated in the heterogeneity of the QT interval [24]. Ultimately, an interesting study suggested that polymorphism of angiotensin-converting enzyme and angiotensin type-1 receptor genes might contribute to the prolonged QTc interval in hemodialysis patients [25].

#### *Effect of Electrolyte Changes*

Another point of debate was the correlation between serum electrolytes – in particular serum potassium and magnesium levels – and the occurrence of QT interval prolongation and increase of QTD after dialysis. In this respect, our findings substantiated evidence from many earlier reports, which demonstrated that the increase of QT interval duration and QTD inversely correlated with serum potassium and/or magnesium levels [8, 26]. Nevertheless, other evidence from some peer-reviewed literature did not support such a correlation [27, 28]. Again, the composition of the dialysis bath may eventually play a pivotal role in this regard. Genovesi et al. [29] compared the effect of 6 dialysis baths with different ion composition on the QTc interval duration after sessions. Not surprisingly, they found that the longest QTc interval duration occurred with the low-potassium/low-calcium dialysate, whereas the shortest occurred with the high-potassium/high-calcium dialysate. Interestingly, they reported an inverse correlation between the QT interval changes and serum potassium and calcium levels, but not with serum magnesium [29]. As a matter of fact, their results would favor a high-potassium/high-calcium dialysis regimen, at least from the safety point of view. Nevertheless, a high-calcium dialysate might predispose to hypercalcemia and vascular calcification, and a high-potassium dialysate might not adequately remove potassium load from the plasma. In another intriguing study, Buemi et al. [30] compared hemodiafiltration with a constant potassium concentration and hemodiafiltration with a variable potassium concentration set at 1 mEq/l less than that in plasma, which gradually decreased throughout the session, maintaining an almost constant plasma-dialysate potassium concentration gradient. Interestingly, they found that post-dialysis QTD was significantly lower in the variable as compared to the constant regimen [30]. Indeed, the variable regimen sustained a constant potassium gradient that effectively achieved a gradual removal of potassium, in contrast to the rapid drop of plasma potassium with the constant regimen, at least early during sessions. Moreover, they found that hyperpolarization of the red cell membrane occurred with the constant but not with the variable regimen, something that could have a destabilizing effect on different types of cardiac cells, inviting reentrant circuits [30].

#### *Clinical Implications*

In view of the highly variable response of the QTc interval duration and QTD to hemodialysis sessions, we believe that the dialysis regimen must be customized in a way that secures the maximal safety for each patient. ECG recording for patients on hemodialysis following each dialysis session would effectively identify patients whose repolarization surrogates increase after sessions. In these patients, we can individually adopt a dialysis regimen which is, reportedly, less likely to affect ventricular repolarization. Assessment of the QT in-

terval measures would offer a simple, rapid, inexpensive, and widely available tool to gauge early changes in ventricular repolarization. In our quest to raise the standard of care for many patients with end-stage renal disease, we would recommend routine measurement of the QTc interval duration and QTD from ECG recorded in the immediate post-dialysis period. Additionally, serum potassium and magnesium levels should be regularly checked and immediately corrected following each dialysis session.

## Conclusion

Our findings suggest a highly variable response of the QTc interval duration and QTD to hemodialysis sessions. The post-dialysis QTc interval duration inversely correlated with the change of both serum potassium and magnesium levels after dialysis.

### *Limitations of the Study*

Our findings are based on a single center study with a relatively small sample size of the cohort, a fact that makes it difficult to draw reliable conclusions. Multicenter studies using the same protocol and examining a larger number of patients are needed for more solid conclusions to be drawn. Besides, measurement of the QT interval should rather be performed automatically, by means of computer software. Finally, the cross-sectional nature of the design which does not infer any causal or temporal relationship necessitates careful interpretation of the results.

## Disclosure Statement

There are no conflicts of interest.

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