ORIGINAL ARTICLE

Long QT, alteration of calcium-phosphate product, prevalence of ventricular arrhythmias and sudden death in peritoneal dialysis patients: a Holter study

QT lungo e alterazioni del prodotto calcio-fosforo, prevalenza di aritmie ventricolari e morte improvvisa in pazienti in dialisi peritoneale: uno studio Holter

Pierluigi Di Loreto a, Claudio Ronco a, Giorgio Vescovo b,*

a Nephrology Dialysis Transplantation Unit, San Bortolo Hospital, Vicenza, Italy
b Internal Medicine Unit, San Bortolo Hospital, Vicenza, Italy

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KEYWORDS
Peritoneal dialysis; Long QT; Ventricular arrhythmias; Calcium phosphate product; Brain natriuretic peptide.

Summary
Materials and methods: We studied 79 patients on peritoneal dialysis. Each underwent 24-h electrocardiography (Holter monitoring) and measurement of the rate-corrected QT interval (QTc). We analyzed the correlation between QTc and plasma levels of Ca++, PO4−, K+, Na+, Mg++, and parathyroid hormone (PTH).

Results: The mean QTc was 0.445 ± 0.04 s. In 55 patients, the QTc was prolonged (> 0.45 s). Mean laboratory values for the group were: PTH 344 ± 25 pg/mL, Ca++ 9.27 ± 0.11 mg/dL, PO4− 5.5 ± 1.5 mg/dL, Na+ 139.6 ± 3.4 mmol/L, K+ 4.04 ± 0.64 mmol/L, and Mg++ 2.52 ± 0.43 mg/dL. Holter monitoring revealed complex premature ventricular contractions in 44 patients, monomorphic premature ventricular contractions in 16, and nonsustained ventricular tachycardia (NSVT) in 10. The QTc was significantly correlated with plasma levels of PO4− (r = 0.045, p < 0.05), PTH (r = 0.077, p < 0.02), and Ca++ (r = 0.076, p < 0.02). Eleven patients had Lown class 4a or 4b ventricular arrhythmias, and their mean QTc was 465 ± 0.02 ms. Ten had NSVT and their QTc was 464 ± 0.03 ms. Eleven patients died suddenly (mean QTc 465 ± 0.03 ms); all 11 had either NSTV or Lown class 4 ventricular arrhythmias.

Conclusions: Long QTc seems to be associated with an increased prevalence of ventricular arrhythmias that may be the cause of sudden cardiac death.

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* Corresponding author: Internal Medicine 1, San Bortolo Hospital, v.le Rodolfi 37 - 36100 Vicenza, Italy.
E-mail: gvescov@yahoo.it (G. Vescovo).

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Introduction

Patients with CKD (Chronic Kidney Disease) in substitutive therapy have an increased cardiovascular risk [1]. During the first year of dialysis 20% of the patients die, 50% and 25% of these are sudden deaths [2]. Ventricular arrhythmias very often represent the final event in dialysis patients. Transient ischemia due to CAD (Coronary Heart Disease) or alterations of electrolytes can trigger arrhythmias on pathological substrates such as myocardial fibrosis or hypertrophy.

We recognise different types of arrhythmias in patients with CKD: ischemic firing arrhythmias, re-entry arrhythmias through fibrotic pathways, torsade de pointes in patients with long QT.

Long QT is present in a substantial number of CKD patients both in haemodialysis and in peritoneal dialysis [3]. The reason for prolonged QT is not clear. It has been attributed to ischemia, autonomic imbalance, acidosis or ionic balance alterations. Because QT varies with heart rate, the correct QT (QTc) is calculated with the Bazzet formula ($QTc = QT/\sqrt{RR}$). Normal QTc is 440 ms in men and 450 ms in women. Usually the longer is QTc, the higher is the risk of developing torsade de pointe. Another marker of arrhythmogenic risk is QT dispersion (difference between the longest and the shortest QT). This represent an index of repolarisation dishomogeneity, that facilitate the occurrence of macro-reentry [4]. Increased QT dispersion has been shown in dialysis patients [5,6]. Beyond genetic abnormalities, there are a number of acquired situations that may cause QTc prolongation: ionic imbalances, co-morbidities such as kidney failure, drugs that increase QT (macrolides, chinolones, antiarrhythmic class Ic and III). There are also gene polymorphisms (i.e., CYP2D6) which characterize fast and slow metabolizers. It has been observed that in haemodialysis patients QT can be rapidly prolonged by hypocalcaemia due to low calcium dialysis solutions [7]. We also know that chronic calcium overload of myocardial cells can produce arrhythmias and uremic subjects have an altered myocardial calcium handling [8]. Chronic acidosis and hypercalcaemia can lead to a cytosolic calcium load [9].

Moreover patients with CKD have elevated values of natriuretic peptides (BNP and NT-proBNP). They increase intracellular cGMP (Cyclic Guanosine Monophosphate) [10] and decrease SERCA (Sarcoplasmic Reticulum Calcium ATPase) activity [11], and have the potential to increase cytosolic Ca++ and trigger arrhythmias.

Aim of this study was to see in a population of patients in chronic peritoneal dialysis whether there was a correlation between QT prolongation, ionic disturbances, BNP concentration and ventricular arrhythmias.

Materials and methods

Patients

Seventy-nine patients in peritoneal dialysis (Department of Nephrology, Vicenza Hospital, Italy) were studied. Exclusion criteria were NIDDM (Non Insulin Dependent Diabites Mellitus), uncontrolled blood pressure, BP ($\geq 140/90$ mmHg at office visit), length of dialysis < 3 months, use of beta-blockers, Class Ic and III antiarrhythmics, CHF (Chronic Heart Failure) NYHA Class $\geq$ II, complete LBBB (Left Bundle Branch Block) and/or RBBB (Right Bundle Branch Block), presence of pacemaker (PM) or permanent atrial fibrillation (AF), alcohol abuse ($> 60$ g/die. which may prolong QTc). QT had to be measurable in at least 8 leads. This led to the exclusion of 26 of the 105 patients forming the whole peritoneal dialysis population.

Dialysis

Dialysis solutions at pH 7.4 contained calcium 1.25 mmol/L, potassium 2 mmol/L, sodium 134 mmol/L, magnesium 0.25 mmol/L, CI 105 mmol/L, lactate 15 mmol/L, bicarbonate 25 mmol/L, glucose 1.5 g/dL.

A blood sample was collected after 10 hours of fasting, in the morning, for measurement of Na’, Ca++, PO4, Mg++, K’, PTH, NT-proBNP. Acid-basis equilibrium, serum albumin, haemoglobin levels and iron stores were also measured. Calcitriol was not given the evening before blood test.

ECG and Holter monitoring

A 12 leads ECG was taken within 1 hour from the execution of blood test, but at least 15 minutes after blood was drawn. ECG tracings were recorded with a Hewlett Packard Page writer 100. ECGs were red by the same cardiologist and QT and QTc’s measured manually from the beginning of QRS complex to the end of T wave taken at isoelectric point. If amplitude of Twave was $< 50$ µV, that lead was excluded from analysis. In the presence of U wave QT was measured at nadir of the trace between Q and T waves (206). When the end of Twave was not well defined the lead was excluded from analysis. All QTs were measured in all the leads and the longest values measured in three consecutive intervals were used for the present analysis. RR interval precedent to that where QT was measured was used to calculate QTc with the Bazzet formula.

Intraobserver variability was 5%.

24 hours Holter monitoring was performed by using a 3 channels, 12 leads recorder (Mortara Rangoni Inc., Casalecchio di Reno, Bologna, Italy). Holters were red automatically with cardiologist supervision. SVCs (Supraventricular Premature Contractions), PVCs (Premature Ventricular Contractions) $> 2/ hour$, NSVT (Non Sustained Ventricular Tachycardia) (defined as $> 3$, $< 15$ PVCs), SVT (Sustained Ventricular Tachycardia) ($\geq 15$ PVCs) were recorded. The Lown classification was used for statistical purposes and for correlations (207).

Patients outcomes

Patients were followed up for 1 year (outpatient visits or telephonically) and all the witnessed and non-witnessed sudden deaths were recorded.

Correlation between biochemical parameters and QTc

We correlated QTc and the following parameters: Na’, Ca++, PO4, Mg++, K’, PTH (Parathyroid Hormone), NT-proBNP, Lown class.
Statistical analysis

Parametric continuous variables have been expressed as mean ± standard deviation (SD). Student t test and linear regression were used. A difference of 5% was considered significant. Analysis was performed with a SPSS Chicago Illinois package.

Results

49 patients were male (62%), 30 (38%) females. Mean age was 60 ± 14.2 years. Causes of end stage renal disease were: chronic glomerulonephritis (24), chronic pyelonephritis (9), hypertension (17), autosomal dominant polycystic kidney disease (15), unknown reason (14).

Dialytic age was 46 ± 10 months.

63 patients (79.7%) were in CAPD (Continuous Ambulatory Peritoneal Dialysis), while 16 (20.3%) were in APD (Automated Peritoneal Dialysis); dualistic efficiency assessed by the Kt/V/weekly ratio was 2.07 ± 0.44, diuresis 1,500 ± 500 cc/day, BMI (Body Mass Index) 26.7 ± 6.7 kg/m².

Biochemical parameters

Haemoglobin was 11.9 ± 1 g/dL, iron 79 ± 16 µg/dL, ferritin 35 ± 13 ng/mL, and transferrin 363 ± 99 µg/mL, transferrin saturation 38 ± 18%, serum albumin 5.7 ± 0.8 g/dL, sNa⁺ 139.6 ± 3.4 mmol/L, sK⁺ 4.04 ± 0.63 mmol/L, sCa²⁺ 9.27 ± 0.11 mg/dL, sPO₄³⁻ 5.5 ± 1.5 mg/dL, sMg²⁺ 2.52 ± 0.43 mg/dL, PTH 344 ± 25 pg/mL, NT-proBNP 6,528 ± 93 pg/mL, pH 7.4 ± 0.2, HCO₃⁻ 28 ± 2mEq/L, PO₂ 94 ± 7 mmHg, PCO₂ 38 ± 4 mmHg.

QTc

Mean QTc duration in our population was 445 ± 0.04 ms.

Taken QTc 0.44 seconds in men and 0.45 seconds in women, as normal values, 33 man (67%) and 22 woman (73%) showed a long QTc.

Correlations between QTc and biochemical parameters

The following significant correlations were found (fig. 1a-c):

- QTc vs PO₄³⁻ $r^2 = 0.045 \ p < 0.05$
- QTc vs Ca²⁺ $r^2 = 0.076 \ p = 0.02$
- QTc vs PTH $r^2 = 0.77 \ p = 0.02$
- QTc vs NT-proBNP $r^2 = 0.057 \ p = 0.02$

Figure 1 Correlation between a) QTc and P, b) QTc and Ca, c) QTc and PTH, d) NT-proBNP and Na.
Holter monitoring detected arrhythmias

The 24 hours Holter monitoring showed the presence of supraventricular arrhythmias in 38 patients, complex PVCs in 44, more than 2 monomorphic PVCs/hour in 16 patients, NSVT in 10 patients. 11 patients were in Lown class 4a or 4b. 11 patients died suddenly and their QTc were 461, 468, 455, 467, 464, 466, 468, 469, 462, 460, 480 ms respectively (mean 465 ± 64 ms). This value was significantly higher than that of the entire casistic (QTc 445 ± 4 ms; p < 0.05) (fig. 2a).

11 patients were in Lown class 4a or 4b (QTc of these patients were 466, 469, 451, 460, 454, 460, 461, 466, 462, 451, 450, 453 ms; mean 465 ± 2 ms; p < 0.05 vs QTc of the entire population: 445 ± 4 ms) (fig. 2b).

10 patients were found to have NSVT. QTc of these patients was 452, 468, 455, 460, 480, 448, 467, 464, 469, 466 ms (464 ± 3 ms, which was significantly longer than that of the entire population (445 ± 4 ms; p < 0.05) (fig. 2c).

All the patients with sudden death were either in Lown class 4 or had NSVT.

Discussion

Long QTc and increased QT dispersion in patients with CHF and CKD represent a risk factor for the development of life threatening arrhythmias. There are reports on alterations of ventricular repolarisation and haemodialysis treatment. Only in 4 studies both haemodialysis and peritoneal dialysis patients were included [12–14]. Wu et al. [15] reported a correlation between QT and tranferrin saturation, arguing that myocardial iron overload induces conduction disturbances leading to arrhythmias and sudden death [16–18].

Peritoneal dialysis patients are different from haemodialysis patients which have more rapid changes of ionic balance as reflected by sudden changes of QT [7,19]. This is not the case of peritoneal dialysis, where fluid exchange is slower leading to less pronounced changes in seric electrolytes [19]. In this population long QT is more related to chronic rather than acute ionic changes and probably less variable over time.

In our population QTc was prolonged in the majority of patients. QTc correlates with Ca, PO4 and PTH, parameters that are usually altered during substitutive therapy. Moreover these patients have very high levels of NT-proBNP, similar to those of patients with systolic CHF (fig. 3: comparison with a population with systolic heart failure with normal kidney function).

NT-proBNP in this population of patients, that have no clinical signs of CHF since NYHA class higher than II were excluded, is elevated for two reasons:

- incapacity of kidney to eliminate NT-pro-BNP;

- QTc vs PTH r² = 0.077 p < 0.02
- QTc vs Ca⁺⁺ r² = 0.076 p < 0.02

We could not find any significant correlation between Na⁺, K⁺, Mg⁺⁺ and QTc, as it was for iron, transferrin saturation and parameters of acid-basis equilibrium.

We also correlated NT-pro-BNP with Na⁺ and QTc (r² = 0.057; p < 0.02; r² = 0.025; p = 0.19 respectively) (fig. 1d).

![Figure 2](image_url)

Figure 2  a) QTc duration in patients with sudden death and whole population (0.465 ± 0.064 s vs 0.445 ± 0.04 s; p < 0.05), b) QTc duration in patients with whole population vs Lown classes 4a and 4b (0.445 ± 0.04 s vs 0.465 ± 0.02 s; p < 0.05), c) QTc duration in patients with NSVT vs whole population (0.464 ± 0.03 s vs 0.445 ± 0.04 s; p < 0.05).
fluid overload deliberately maintained in order to favour peritoneal exchanges. This is also confirmed by the correlation between serum Na and NT-proBNP. BNP by itself is able to increase intracellular calcium in myocytes by activating cGMP [20]. This can be even more pronounced if the serum Ca concentration is elevated. Moreover BNP decreases SERCA activity [11] contributing to increase cytosolic calcium [21], that is arrhythmogenic [22,23]. Whether the increased cytosolic calcium could also contribute to QTc prolongation, it remains to be established, although the correlation between serum Ca and QTc seems to support this hypothesis. In our patients any correlation was found between QTc and parameters of iron metabolism; this may be due to the fact that these patients have sometimes preserved diuresis and better response to erythropoietin treatment [24]. We could not find either correlations between QTc or parameters of acid-basis equilibrium, in this case it seems also plausible that these patients have very little change of the equilibrium which is corrected slowly throughout the whole day as indicated by KT/V. The relationship between changes in repolarisation and calcemia and PTH is well known [7,25], but we describe for the first time a correlation between QTc and hyperphosphataemia [26,27]. This sheds some light on the importance of controlling calcium-phosphorus metabolism in patients with renal replacement therapy. To correct hyperparathyroidism it is important not to exceed with calcium acetate and carbonate: this may produce increased levels of serum calcium, intracellular calcium overload and deleterious consequences in terms of myocyte arrhythmogenicity. The dose of calcium should not exceed 1.5 g/die. Calcitriol should be carefully dosed avoiding hypercalcaemia, hyperphosphoraemia and excessive PTH suppression. More recent therapies with phosphate binders as sevelamer and lanthanum may have a better impact on intracellular calcium levels, as it may be with calcium mimetics.

Patients with longer QTc have more ventricular arrhythmias in terms of Lown class. Patients who experienced sudden death, that is most probably arrhythmic, had longer QTc, higher Lown class and more episodes of NSVT. We can hypothesize that long QT has an important role in the genesis of arrhythmias and sudden death.

Although the mechanism of QT prolongation is not entirely clear, our data suggest a link with serum calcium, phosphorus and PTH. The alteration of calcium-phosphorus metabolism may be also responsible for the electrophysiological abnormalities.

Myocyte calcium overload can trigger arrhythmias as reflection of elevated serum calcium and increased BNP levels. Increased intracellular calcium could also contribute to QT prolongation [28–30].

We can therefore conclude that tight control of calcium, phosphorus and PTH is essential. The use of drugs that may prolong QT must be avoided (fluoroquinolones, macrolids, antiarrhythmics such as sotalol [31], amiodarone [32] and flecaïnide). The use of phosphate binders containing calcium has to be carefully weighed in order to avoid potential increase of serum and intracellular calcium.

These preliminary data need to be confirmed in larger randomized prospective studies. A comparison between peritoneal and haemodialysis patients is needed to prove the hypothesis that alterations of calcium phosphorus metabolism are responsible for altered repolarisation and malignant arrhythmias. It remains also to be established whether elevated levels of BNP may worsen or trigger arrhythmias. In case a close monitoring of QTc and natriuretic peptides may have a clinical significance in order to prevent sudden death in patients in replacement therapy.

Conflict of interest

The study reported in this manuscript has received funding from Veneto Region.

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