Italian Journal of Medicine (2012) 6, 99—104

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/itjm

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*

Received 10 January 2011; accepted 23 February 2011
available online 29 April 2011

**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 $0.445 \pm 0.04$ s. In 55 patients, the QTc was prolonged (> 0.45 s). Mean laboratory values for the group were: PTH $344 \pm 25$ pg/mL, $Ca^{++}$ $9.27 \pm 0.11$ mg/dL, $PO4^{-}$ $5.5 \pm 1.5$ mg/dL, $Na^{+}$ $139.6 \pm 3.4$ mmol/L, $K^{+}$ $4.04 \pm 0.64$ mmol/L, and $Mg^{++}$ $2.52 \pm 0.43$ 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 $465 \pm 0.02$ ms. Ten had NSVT and their QTc was $464 \pm 0.03$ ms. Eleven patients died suddenly (mean QTc $465 \pm 0.03$ 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.


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

1877-9344/$ — see front matter © 2011 Published by Elsevier Srl.
doi:10.1016/j.itjm.2011.02.010

## 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, acid-basis or ionic balance alterations. Because QT varies with heart rate, the correct QT (QTc) is calculated with the Bazzet formula ($QT/\sqrt{^2}RR$). 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 point. 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 macroreentry [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 cytolsolic $Ca^{++}$ 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 Daibetes 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 $>$ 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, Cl 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 Twave taken at isoelectric point. If amplitude of Twave was $<$ 50 $\mu$V, that lead was excluded from analysis. In the presence of U wave QT was measured at nadir of the trace between Q and Twaves (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 QTwas 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, Utaly). Holters were red automatically with cardiologist supervision. SVPCs (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 (Parathytoid 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 pielonephritis (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 Ambulatorial 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/m$^2$.

### 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, $sCa^{++}$ 9.27 ± 0.11 mg/dL, $sPO4^-$ 5.5 ± 1.5 mg/dL, $sMg^{++}$ 2.52 ± 0.43 mg/dL, PTH 344 ± 25 pg/mL, NT-proBNP 6,528 ± 93 pg/mL, pH 7.4 ± 0.2, $HCO_3^-$ 28 ± 2mEq/L, $PO_2$ 94 ± 7 mmHg, $PCO_2$ 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 $PO4^-$ $r^2 = 0.045$ $p < 0.05$

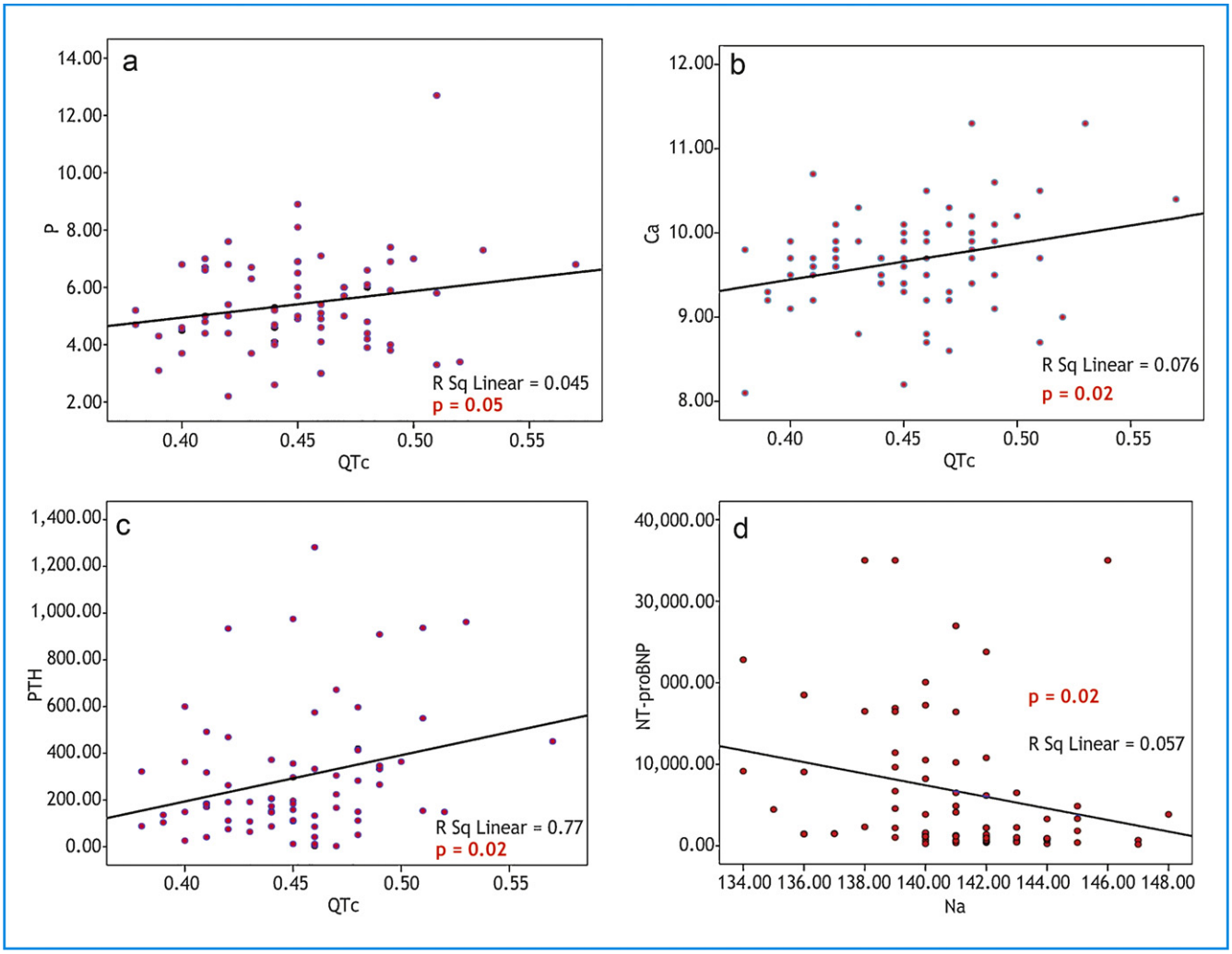


**Figure 1** Correlation between a) QTc and P, b) QTc and Ca, c) QTC and PTH, d) NT-proBNP and Na.

- QTc vs PTH $r^2 = 0.077$ $p < 0.02$
- QTc vs $Ca^{++}$ $r^2 = 0.076$ $p < 0.02$

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 ($r^2 = 0.057$; $p < 0.02$; $r^2 = 0.025$; $p = 0.19$ respectively) (*fig. 1d*).

## 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 $465 \pm 64$ ms). This value vas significantly higher than that of the entire casistic (QTC $445 \pm 4$ ms; $p < 0.05$) (*fig. 2a*).

11 patients were in Lown class 4a o 4b (QTc of these patients were 466, 469, 451, 460, 454, 460, 461, 466, 462, 451, 450, 453 ms; mean $465 \pm 2$ ms; $p < 0.05$ vs QTc of the entire population: $445 \pm 4$ 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 ($464 \pm 3$ ms, which was significantly longer than that of the entire population ($445 \pm 4$ 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;

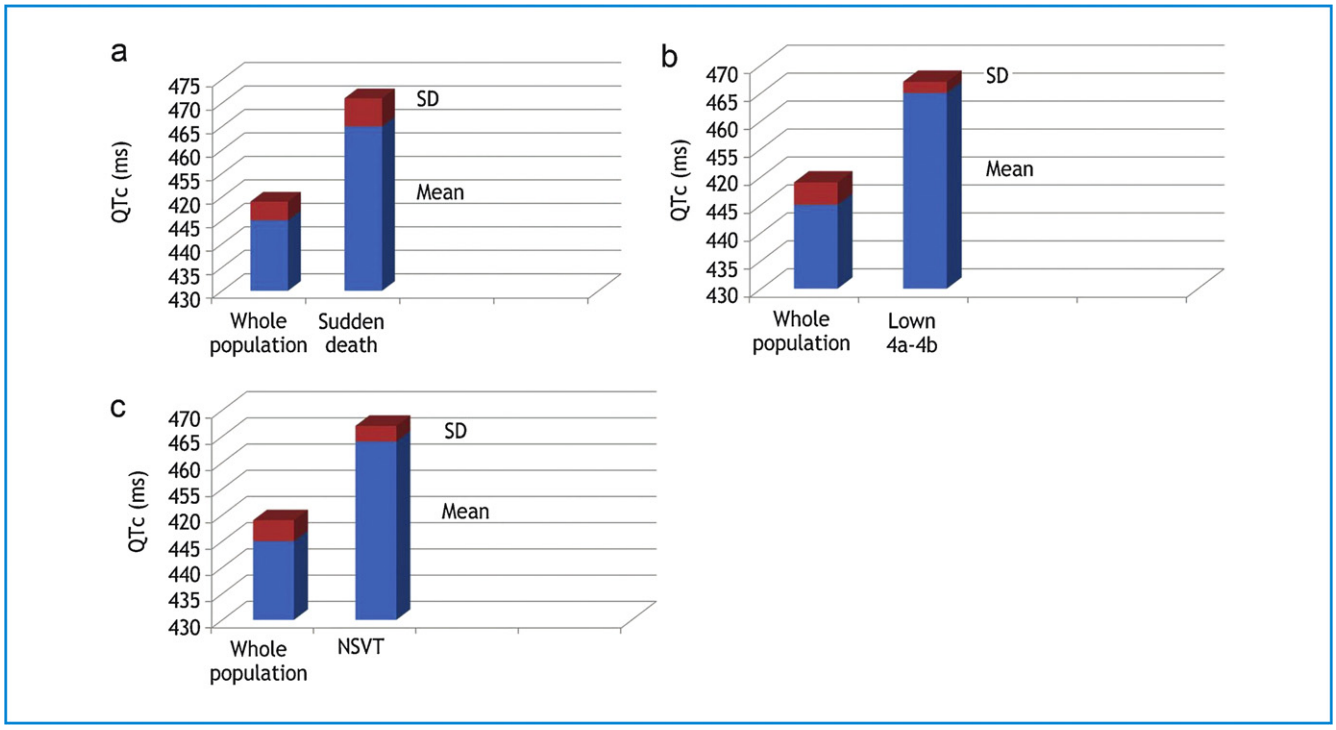


**Figure 2** a) QTc duration in patients with sudden death and whole population ($0.465 \pm 0.064$ s vs $0.445 \pm 0.04$ s; $p < 0.05$), b) QTc duration in patients with whole population vs Lown classes 4a and 4b ($0.445 \pm 0.04$ s vs $0.465 \pm 0.02$ s; $p < 0.05$), c) QTc duration in patients with NSVT vs whole population ($0.464 \pm 0.03$ s vs $0.445 \pm 0.04$ s; $p < 0.05$).

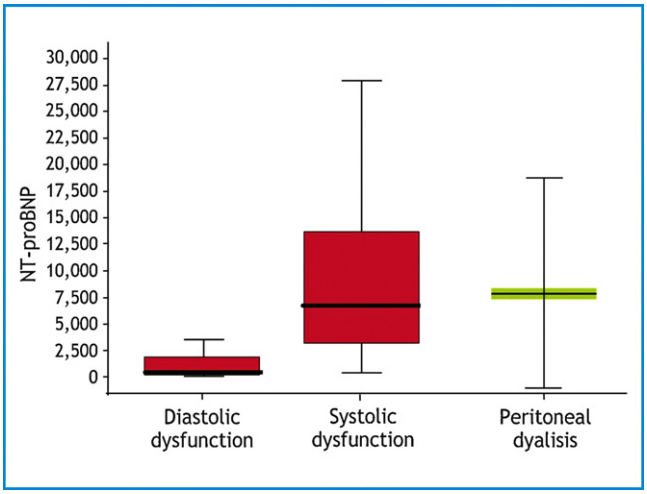


**Figure 3** Comparison between NT-proBNP (pg/mL) in systolic dysfunction (N = 150), diastolic dysfunction (N = 130), peritoneal dialysis (N = 79) ($\chi^2$ p = NS peritoneal dialysis vs CHF both).

- 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 calcaemia 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 (fluorochinolons, macrolids, anthiarrhythmics such as sotalol [31], amiodarone [32] and flecainide). 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 this 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.

## References

[1] Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 2002;13(7):1918—27.
[2] Chazan JA. Sudden death in patients with chronic renal failure on haemodialysis. Dial Transplant 1987;16:447—8.
[3] Covic A, Diaconita M, Gusbeth-Tatomir P, Covic M, Botezan A, Ungureanu G, et al. Haemodialysis increases QT(c) interval but not QT(c) dispersion in ESRD patients without manifest cardiac disease. Nephrol Dial Transplant 2002;17(12):2170—7.
[4] Hii JT, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Precordial QT interval dispersion as a marker of torsade de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 1992;86(5):1376—82.
[5] Gussak I, Gussak HM. Sudden cardiac death in nephrology: focus on acquired long QT syndrome. Nephrol Dial Transplant 2007;22(1):12—4.
[6] Nakamura S, Ogata C, Aihara N, Sasaki O, Yoshihara F, Nakahama H, et al. QTc dispersion in haemodialysis patients with cardiac complications. Nephrology (Carlton) 2005;10(2):113—8.
[7] Näppi SE, Virtanen VK, Saha HH, Mustonen JT, Pasternack AI. QTc dispersion increases during hemodialysis with low-calcium dialysate. Kidney Int 2000;57(5):2117—22.

[8] McMahon AC, Vescovo G, Dalla Libera L, Wynne DG, Fluck RJ, Harding SE, et al. Contractile dysfunction of isolated ventricular myocytes in experimental uraemia. Exp Nephrol 1996;4(3): 144—50.
[9] Harding SE, MacLeod KT, Jones SM, Vescovo G, Poole-Wilson PA. Contractile responses of myocytes isolated from patients with cardiomyopathy. Eur Heart J 1991;12(Suppl D):44—8.
[10] Kuhn M. Structure, regulation, and function of mammalian membrane guanylyl cyclase receptors, with a focus on guanylyl cyclase-A. Circ Res 2003;93(8):700—9.
[11] Kögler H, Schott P, Toischer K, Milting H, Van PN, Kohlhaas M, et al. Relevance of brain natriuretic peptide in preload-dependent regulation of cardiac sarcoplasmic reticulum Ca2+ ATPase expression. Circulation 2006;113(23):2724—32.
[12] Beaubien ER, Pylypchuk GB, Akhtar J, Biem HJ. Value of corrected QT interval dispersion in identifying patients initiating dialysis at increased risk of total and cardiovascular mortality. Am J Kidney Dis 2002;39(4):834—42.
[13] Kantarci G, Ozener C, Tokay S, Bihorac A, Akoğlu E. QT dispersion in hemodialysis and CAPD patients. Nephron 2002;91(4): 739—41.
[14] Yildiz A, Akkaya V, Sahin S, Tükek T, Besler M, Bozfakioglu S, et al. QT dispersion and signal-averaged electrocardiogram in hemodialysis and CAPD patients. Perit Dial Int 2001;21(2): 186—92.
[15] Wu VC, Huang JW, Wu MS, Chin CY, Chiang FT, Liu YB, et al. The effect of iron stores on corrected QT dispersion in patients undergoing peritoneal dialysis. Am J Kidney Dis 2004;44(4): 720—8.
[16] Genovesi S, Dossi C, Viganò MR, Galbiati E, Prolo F, Stella A, et al. Electrolyte concentration during haemodialysis and QT interval prolongation in uraemic patients. Europace 2008;10(6): 771—7.
[17] Kuryshev YA, Brittenham GM, Fujioka H, Kannan P, Shieh CC, Cohen SA, et al. Decreased sodium and increased transient outward potassium currents in iron-loaded cardiac myocytes. Implications for the arrhythmogenesis of human siderotic heart disease. Circulation 1999;100(6):675—83.
[18] Schwartz KA, Li Z, Schwartz DE, Cooper TG, Braselton WE. Earliest cardiac toxicity induced by iron overload selectively inhibits electrical conduction. J Appl Physiol 2002;93(2): 746—51.
[19] Yetkin E, Ileri M, Tandoğan I, Boran M, Yanik A, Hisar I, et al. Increased QT interval dispersion after hemodialysis: role of peridialytic electrolyte gradients. Angiology 2000;51(6):499—504.
[20] Margulies KB, Burnett Jr JC. Visualizing the basis for paracrine natriuretic peptide signaling in human heart. Circ Res 2006; 99(2):113—5.
[21] Wollert KC, Yurukova S, Kilic A, Begrow F, Fiedler B, Gambaryan S, et al. Increased effects of C-type natriuretic peptide on contractility and calcium regulation in murine hearts overexpressing cyclic GMP-dependent protein kinase I. Br J Pharmacol 2003;140(7):1227—36.
[22] Yee A, Wang M. Cardiovascular risk factors in peritoneal dialysis revisited. Perit Dial Int 2007;27(Suppl 2):228—32.
[23] Kimura K, Tabei K, Asano Y, Hosoda S. Cardiac arrhythmias in hemodialysis patients. A study of incidence and contributory factors. Nephron 1989;53(3):201—7.
[24] Ramirez G, Brueggemeyer CD, Newton JL. Cardiac arrhythmias on hemodialysis in chronic renal failure patients. Nephron 1984;36(4):212—8.
[25] Strata G, Limbruno U, Leoncini GP, Di Vincenzo A, Palla R, Mariani M. Physiopathology of cardiac arrhythmias in end-stage renal disease. Contrib Nephrol 1994;106:30—5.
[26] Di Loreto P, Vescovo G, Crepaldi C. QTc duration in patients in peritoneal dialysis: correlation with biochemical parameters. Paper presented at World Congress of Nephrology, Milan; May 22—26, 2009.
[27] Di Loreto P, Martino F, Crepaldi C. Long QTc, alterations of calcium phosphate products: prevalence of ventricular arrhythmias and sudden death in peritoneal dialysis patients: an Holter study. Paper presented at American Society of Nephrology Annual Meeting, Denver; November 16—21, 2010.
[28] Topol EJ. Nesiritide — not verified. N Engl J Med 2005;353(2): 113—6.
[29] Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105(20): 2392—7.
[30] Němec J, Kim JJ, Gabris B, Salama G. Calcium oscillations and T-wave lability precede ventricular arrhythmias in acquired long QT type 2. Heart Rhythm 2010;7(11):1686—94.
[31] Sharma PP, Sarma JS, Singh BN. Effects of sotalol on the circadian rhythmicity of heart rate and QT intervals with a noninvasive index of reverse-use dependency. J Cardiovasc Pharmacol Ther 1999;4(1):15—21.
[32] Riera AR, Uchida AH, Ferreira C, Ferreira Filho C, Schapachnik E, Dubner S, et al. Relationship among amiodarone, new class III antiarrhythmics, miscellaneous agents and acquired long QT syndrome. Cardiol J 2008;15(3):209—19.