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Impact of Vascular Calcification on Corrected QT Interval at the Time of Renal Transplantation

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Key Words
QT interval · Chronic kidney disease stage V · Dialysis · Vascular calcification

Abstract
Background/Aims: Sudden death is the major cause of cardiac mortality in dialysis patients, accounting for approximately 60% of cardiovascular deaths. A prolonged QT interval and arterial calcification have been associated with increased cardiovascular morbidity and mortality in different patient populations including patients with chronic kidney disease (CKD). In the present study, we aimed to elucidate the association of vascular calcification with corrected QT interval duration in patients with end-stage renal disease. ***Methods:*** We performed a single-center cross-sectional study in patients referred for renal transplantation. Patients taking QT-prolonging agents or with conduction abnormalities were excluded. Aortic calcifications were scored by means of lumbar X-rays. ***Results:*** In the final analysis, 193 patients (118 men, 52 years old) were included. A prolonged QT interval was observed in 26% of the patients. Multivariate analysis showed an independent and direct association between corrected QT duration and the extent of aortic calcifications ($p = 0.0004$) independent of age, gender, cardiovascular history, electrolytes and parameters of mineral metabolism. ***Conclusions:*** A prolonged QT interval is prevalent in patients with CKD stage 5D. Aortic calcification is associated with a prolonged QT duration, independent of traditional determinants.

Introduction

Cardiovascular (CV) disease is the main cause of death in patients with chronic kidney disease (CKD). However, ischemic cardiac disease comprises only a minority of the CV-related deaths. Approximately 60% of all cardiac deaths and 25–39% of all-cause mortality in patients on dialysis are due to sudden cardiac death [1]. In addition to the traditional risk factors, several nontraditional risk factors may contribute to the increased risk of sudden cardiac death in this patient population. These include left ventricular hypertrophy (LVH), abnormalities in the myocardial ultrastructure and function, and rapid electrolyte and fluid shifts [2, 3].

Prolonged ventricular depolarization and repolarization, assessed from resting electrocardiogram (ECG), predict morbidity and mortality in the healthy population [4]. In patients with CKD, results regarding outcome are conflicting [5, 6]. The association between QT dura-

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tion and CV disease has been stated to reflect a relationship between abnormal repolarization and sudden death. Moreover, QT interval duration is associated with subclinical atherosclerosis indicating that the presence of ischemic heart disease may lead to structural and electrophysiological changes that could prolong QT duration [7].

Furthermore, CKD patients show a very high prevalence of vascular and valvular calcification and these are associated with increased adverse outcomes [8]. Supported by recent data obtained in diabetics and patients with coronary artery disease, we advanced the hypothesis that vascular calcification is associated with a disturbed ventricular depolarization and repolarization in CKD patients [9, 10].

Patients and Methods

Study Population

We performed a cross-sectional study including patients with CKD stage 5 referred for renal or renal/pancreas transplantation at the University Hospitals Leuven between October 2006 and February 2009. The study adhered to the principles of the Declaration of Helsinki and was approved by the ethical committee of the Catholic University of Leuven (www. clinicaltrials.gov; NCT00547040). All subjects provided signed informed consent. Patients taking QT-prolonging agents and patients with a history of pacemaker implantation, atrial fibrillation and conduction abnormalities were excluded. To identify drugs that prolong the QT interval the list from the Arizona Center for Education and Research on Therapeutics was used (http://www.azcert.org). Clinical data extracted from the electronic medical files included usage of beta-blockers, phosphate binders, dose of elemental calcium, age, BMI, dialysis duration, dialysis modality, gender, smoking status, vascular history, diabetes and hypertension. We also calculated the daily elemental calcium dose. CV history was defined as the occurrence of angiographically significant stenosis, myocardial infarction, percutaneous coronary artery intervention, cardiac surgery, peripheral artery disease, cerebrovascular disease or significant stenosis on carotid ultrasound. Tobacco use was categorized as 'none', 'past' or 'current' smoking. Hyperlipidemia was defined as LDL cholesterol >100 mg/dl, total cholesterol >200 mg/dl or being on lipid-lowering drug therapy.

Biochemical Analysis

Serum samples were collected immediately before transplantation (random, nonfasting). Hematocrit, potassium, corrected calcium, phosphorus, magnesium and HbA_{1c} were all measured using standard laboratory techniques. Serum albumin was measured by capillary zone electrophoresis. Serum concentrations of parathyroid hormone were determined by an immunoradiometric assay (normal values: 3–40 ng/l). Calcitriol and $25(OH)D_3$ (calcidiol) levels were measured using a radioimmunoassay. The measured serum calcium levels were adjusted to albumin levels. Serum full-length FGF-23 levels were determined with a sandwich ELISA using two kinds of monoclonal antibodies requiring the simultaneous presence of both the N-terminal and C-terminal portions of FGF-23 (Kainos Laboratories Inc., Tokyo, Japan). This assay differs from the C-terminal assay (Immutopics, USA), which recognizes both full-length and processed C-terminal fragments of FGF-23. FGF-23 levels determined in healthy controls (n = 58) with the full-length FGF-23 assay amounted to 26.3 ± 0.82 ng/l.

Electrocardiographic Variables

Resting 12-lead ECGs were recorded in the supine position. QT intervals were processed using the Marquette 12SL ECG analysis program. QT intervals were corrected for heart rate using Bazett's equation ($QTc = QT/\sqrt{RRinterval}$). Bazett's adjustment does not fully account for the impact of heart rate, particularly in the setting of QRS prolongation. Analysis of the QTc was restricted to participants without left or right bundle branch block. In order to correct for ventricular conduction defects, the JTc interval (QTc interval-QRS duration) was incorporated. Prolonged QTc intervals were defined as ≥450 ms for men and ≥460 ms for women. The presence of LVH was assessed manually by K.J.C. using the Sokolow-Lyon criteria.

Aortic Calcification

Calcification of the aorta was scored using a previously validated system [11] in which both the location and the severity of calcific deposits at each lumbar vertebral segment (L_1–L_4) were evaluated (aortic calcification score) with a maximum score of 24. Lateral lumbar radiographs were analyzed in a blinded fashion by S.H.

Statistical Analysis

Parametric and nonparametric parameters are expressed as mean ± SD and median (minimum-maximum), respectively. Simple between-group comparisons were made using the Mann-Whitney U test for continuous outcome variables and χ^2 or Fisher's exact tests for categorical variables. Correlations were assessed by Spearman's correlation index. Univariate and multivariate regression analyses were performed to identify the parameters associated with QTc. All statistical calculations were carried out using SAS version 9.2 (SAS Inc., Cary, N.C., USA).

Results

Patient Population

Three hundred and four patients with end-stage renal disease were referred for kidney or combined kidney-pancreas transplantation. Sixty-three patients were excluded because of refusal (n = 35) or missing data for either ECG or lumbar X-ray (n = 28). Patients with conduction abnormalities (n = 11), atrial fibrillation (n = 7), pacemaker implantation (n = 2) and QT-prolonging agents (n = 28) were excluded. One hundred and ninety-three patients were eligible for final analysis.

Relevant clinical characteristics of the study population are summarized in table 1. The majority of patients

Table 1. Baseline demographic and laboratory characteristics according to prolonged QT interval

Variable	Total patient population	Prolonged QT interval		p value
		yes (n = 49; 26%)	no (n = 144; 74%)	
Male gender, %	61	67	60	0.3
Presence calcification, %	57	75	50.7	0.0024
Dialysis type, %				
Peritoneal dialysis	26.4	25.5	26.4	
Hemodialysis	71.5	73.5	70.8	0.5
No	2.1	0	2.8	
Beta-blockade, %	43.4	38	45	0.45
Elemental calcium, g/day	0.8 (0–4.8)	0.8 (0–4.8)	1 (0–4.8)	0.45
Cardiovascular history, %	17.1	28.6	13.2	0.013
Hypertension, %	75.5	75	75	0.99
Diabetes, %	13.5	16	13	0.55
Never smokers, %	50	45	52	0.4
Age, years	52 (19–77)	54 (24–75)	52 (19–77)	0.26
Dialysis duration, days	1,122 (0–4,682)	1,097 (0–3,410)	1,171 (0–4,682)	0.96
BMI	25 ± 4	25.6 ± 3.9	24.8 ± 4	0.22
Hct	0.39 ± 0.046	0.40 ± 0.044	0.38 ± 0.05	0.008
Corrected calcium, mmol/l	2.2 (1.5–2.7)	2.1 (1.5–2.4)	2.2 (1.6–2.7)	0.03
FGF-23, ng/l	2,395 (19–58,048)	2,029 (87–37,286)	2,699 (19–58,048)	0.256
Phosphorus, mmol/l	4.4 (1.4–9)	4.34 (2.2–8)	4.4 (1.4–9)	0.9
Total cholesterol, mmol/l	4.5 ± 1.19	4.9 ± 1.2	4.36 ± 1.2	0.002
Magnesium, mmol/l	0.94 ± 0.15	0.94 ± 0.15	0.97 ± 0.15	0.27
Potassium, mmol/l	4.5 (3.1–7.2)	4.2 (3.1–6.5)	4.5 (3.1–7.2)	0.12
Albumin, g/l	46.2 ± 5.1	46.93 ± 5.7	45.89 ± 4.9	0.35
HbA_{1c}	0.05 (0.05–0.09)	0.06 (0.05–0.08)	0.05 (0.05–0.09)	0.2
PTH, ng/l	126.6 (0.09–834.5)	153.3 (4.2–834.5)	115.2 (0.09–510.7)	0.02
25-OH-Vit D, nmol/l	76.6 (11.2–232.9)	74.6 (11.2–232.9)	77.3 (16.5–223.9)	0.87
1,25-diOH-Vit D, pmol/l	60.8 (23.4–243.6)	64.5 (23.4–153.4)	59 (23.4–243.6)	0.21
Bicarbonate, mmol/l	24.5 ± 2.9	24.5 ± 2.9	24.45 ± 2.9	0.9
Aortic calcification score	1 (0–21)	5 (0–21)	1 (0–20)	0.006
Heart rate, beats/min	75 (51–117)	78 (59–117)	73 (51–113)	0.005

Data are expressed as means ± SD or medians (minimum–maximum). Differences between patients with and without an event were assessed by the Mann-Whitney U test, χ^2 or Fisher's exact tests.

were on hemodialysis (71.5%). Forty-three percent of patients were calcification free. The majority of patients were on phosphate binder therapy (96%). Eighty-four percent of these patients were treated with a calcium-containing phosphate binder. The corresponding elemental calcium intake averaged 0.8 g (0–4.8 g/day). Thirty-six percent of patients were treated with a combination of calcium-containing and calcium-free phosphate binders.

We found a prolonged QTc interval in 49 patients (26%). The latter were more likely to have aortic calcification (fig. 1) and prior CV events. Patients with a prolonged QTc, in addition, were characterized by higher hematocrit and parathyroid hormone (PTH) levels and a lower calcium level.

Determinants of QTc and JTc Interval

In univariate linear regression analysis, female gender, age, BMI, known vascular history, and hematocrit and aortic calcification scores were all directly associated with QTc, whereas potassium, corrected calcium, FGF-23 and phosphorus levels were inversely associated with QTc (table 2). In multivariate linear regression analysis, female gender, a higher aortic calcification score, hematocrit and PTH levels and lower calcium and potassium levels were found to be independently associated with QTc. These variables explain 21% of the variability of QTc. Similar associations were found for JTc.

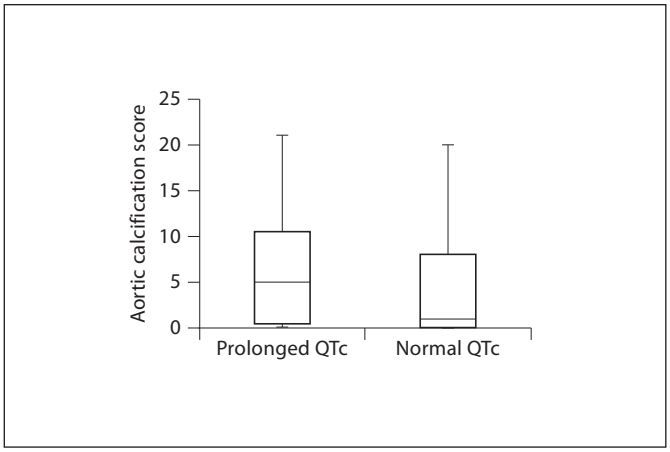

Fig. 1. Aortic calcification score in patients with prolonged and normal QTc.

Table 2. Univariate linear regression analysis of QTc interval with demographic and laboratory variables

Variable	PE	p	R^2
Aortic calcification score	1.12	0.0017	0.045
BMI	1.4	0.047	0.005
Male gender	–7.9	0.05	0.014
Hematocrit	98	0.02	0.02
Corrected calcium	–7.7	0.0027	0.04
logFGF-23	–3.1	0.018	0.03
Potassium	–6	0.024	0.02
Phosphorus	–3.2	0.024	0.021
Total cholesterol	0.1	0.01	0.027
CV history	12.24	0.02	0.02
Age	0.3	0.032	0.024

PE = Parameter estimate.

Analysis by Gender

Table 3 summarizes the main differences between the male and female cohorts. Although we did not find a significant difference in calcification scores between male and female patients, there were distinct differences between the groups. In the male group we found more patients with CV history, hypertension, current and former smokers, higher phosphorus, and higher dose of elemental calcium and albumin. The male patients had lower heart rates and calcium levels.

When we repeated the linear regression analysis in the male and female subgroups, we found that an association between QTc and calcification score was only observed in female patients. Remarkably, in the multivariate analysis the aortic calcification score was the only variable associated with QTc duration. In the male patient population there was a trend of an association between QTc and calcification ($p = 0.06$) in the univariate model, which disappeared in the multivariate model.

Discussion

The main finding of the present study is that there is a positive association of aortic calcifications with QTc interval duration in CKD subjects at the time of renal transplantation.

In this analysis, the prevalence of vascular calcification was 57% which is rather low compared to other trials. In the recently published CORD trial, 81% of patients had evidence of calcification on plain radiography [12]. Furthermore, although the prevalence of a prolonged QT interval in our cohort was high compared to the reported prevalence in healthy individuals (6–8%), it was rather low compared to other trials including CKD patients [4, 9, 10, 13]. There may be several reasons for this discrepancy including the fact that all patients enrolled in the present study were CKD patients eligible for transplantation and thus qualified as free from active cardiovascular disease. Furthermore, patients taking QT-prolonging agents and patients with conduction and rhythm abnormalities were excluded. It should also be noted that our patient population had a rather low prevalence of diabetes (13.5%), which is a known risk factor for calcification. Consequently, the patients enrolled represented a highly selected population.

To the best of our knowledge, only one study so far has reported on the association between QT duration and arterial calcification in renal patients. Di Iorio et al. [14] found an association between QT dispersion, but not QTc interval duration and arterial calcifications. However, the study included patients at different stages of CKD and was hampered by the small sample size.

The mechanisms underlying the positive association between QT duration and arterial calcification remain largely obscure. Long QT intervals may reflect either an increased left ventricular mass, impaired left ventricular function, nonviable myocardium, calcification of the conduction system or a combination of these factors [15].

Several lines of evidence suggest that LVH may be the link between arterial calcification and long QT [10, 15,

Table 3. Baseline demographic and laboratory characteristics according to gender

Variable	Female (n = 75; 39%)	Male (n = 118; 61%)	p value
Presence calcification, %	50.7	61	0.16
Dialysis type, %			
Peritoneal dialysis	29.3	24.6	
Hemodialysis	70.7	72	0.55
No	0	3.4	
Beta-blockade, %	39.2	46.2	0.3
Elemental calcium, g/day	0.8 (0–4)	1.2 (0–4.8)	0.01
Cardiovascular history, %	4	25.4	0.0001
Hypertension, %	64.8	82.2	0.006
Diabetes, %	12.1	14.4	0.4
Never smokers, %	64	41.5	0.002
Prolonged QT, %	21.3	27.9	0.3
Age, years	52 (24–76)	52 (19–77)	0.9
Dialysis duration, days	1,238 (0–4,493)	1,018 (0–4,682)	0.36
BMI	25.3 ± 4.77	24.9 ± 3.53	0.84
Hct	0.38 ± 0.047	0.39 ± 0.046	0.58
Corrected calcium, mmol/l	2.2 (1.6–2.7)	2.2 (1.5–2.7)	0.03
FGF-23, ng/l	1,598 (19–53,090)	2,842 (87–58,048)	0.32
Phosphorus, mmol/l	4.3 (1.8–7.9)	4.7 (1.4–9)	0.0073
Potassium, mmol/l	4.5 (3.2–6.5)	4.5 (3.1–7.2)	0.23
Total cholesterol, mmol/l	4.8 ± 1	4.3 ± 1.3	0.0006
Magnesium, mmol/l	0.95 ± 0.1	0.96 ± 0.2	0.34
Albumin, g/l	45.5 ± 5.2	46.6 ± 5	0.22
HbA1c	0.05 (0.05–0.08)	0.05 (0.05–0.09)	0.013
PTH, ng/l	130.4 (0.09–834.5)	120.4 (0.09–651.4)	0.65
25-OH-Vit D, nmol/l	76.6 (13.7–223.9)	76 (11.2–232.9)	0.75
1,25-diOH-Vit D, pmol/l	64.4 (23.4–172.9)	58.1 (23.4–243.6)	0.19
Aortic calcification score	1 (0–21)	2 (0–21)	0.78
Heart rate, beats/min	79 (59–117)	72 (51–114)	0.0032
QTc, ms	442.5 ± 24.1	434.5 ± 29.1	0.033
JTc, ms	356 ± 25	344.13 ± 29.2	0.0021

Data are expressed as means ± SD or medians (minimum–maximum). Differences between patients with and without an event were assessed by the Mann-Whitney U test, χ^2 or Fisher's exact tests.

16]. It has been reported repeatedly that the degree of arterial calcification correlates with arterial stiffness and the progression of LVH [17, 18].

Not only LVH but also intermyocardial cell fibrosis and capillary loss are highly prevalent in dialysis patients and this may lead to inhomogeneity of both myocardial repolarization and depolarization [16, 19]. In a population-based study, an association was found between pulse wave velocity, as a marker of arterial stiffness, and QT interval prolongation [20]. Unfortunately, left ventricular mass data assessed by echocardiogram or magnetic resonance imaging are missing in the present study. We failed to find an association between ECG-estimated LVH and QT interval, but the relatively small sample size warrants caution and confirmatory data.

Interestingly, we observed a positive association between PTH and QTc duration independent of the calcium level. This finding corroborates the data reported by Amann et al. [21]. These authors very elegantly demonstrated a permissive role of PTH in fibroblast activation and the genesis of the cardiac fibrosis of uremia. Limited data also suggest a direct effect of PTH on electrophysiological changes [22].

Of special interest is the gender difference we found. Women generally have a longer QT interval and sex hormones are thought to play a role in this difference. Several studies have reported a gender difference in left ventricular adaptation to chronic pressure overload with women having a greater increase in the prevalence of LVH and of concentric geometry with progressive aging

[23]. Furthermore, LVH has a greater impact on survival in women [24]. In dialysis patients, conflicting data exist on the association of gender and LVH [16, 25]. Our data support the gender difference in vascular adaptation to reduced arterial compliance. However, the lack of accurate data on left ventricular mass and the relatively small subgroup populations warrants caution and confirmatory data.

Several other limitations of our study need to be acknowledged. First, the cross-sectional nature of our study and the lack of outcome data allow no conclusion on the causality of the association. Second, the biochemical and ECG variables were assessed at the time of transplantation, which implies different time periods since the end of the last hemodialysis session. Conflicting data exist on the change of QTc duration after a dialysis session [13, 26]. However, we are convinced that this will not substantially change the results because we adjusted for serum electrolytes, the main determinants of QTc duration change after hemodialysis.

In conclusion, we found a significant relationship between QTc interval duration and aortic calcification in patients at time of renal transplantation, particularly in the female subgroup. We suggest that this finding is clinically important since both the QTc interval duration and aortic calcification are predictors of CV events and mortality in different patient populations including patients with end-stage renal disease [5, 8, 27]. Further research is necessary to confirm our data, to elucidate the pathophysiology underlying the association between arterial calcification and long QT and to further clarify the clinical implication of long QT specifically in the setting of CKD.

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