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Change in QTC Interval after Kidney Transplantation; Mechanisms and Outcomes

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Abstract

Prolongation of the QTc interval is a predictor of adverse cardiovascular outcomes in patients with end-stage kidney disease undergoing maintenance dialysis. The purpose of our study was to assess change in QTc intervals after kidney transplantation, and to derive insights into the mechanism and consequence of observed changes.

A retrospective chart review was performed on 309 kidney transplant recipients to assess QTc interval changes from baseline, recorded 1 day prior to transplant, to 2 days, 2 weeks, 1 month, 3 months, and 6 months post-transplant. Cardiac deaths occurring within the first year after transplantation were assessed.

Prolonged QTc was present in 36.6% of the cohort. There was a rapid shortening of mean QTc interval evident as early as 2 days post-transplant [mean QTc decrease of 13.2 ms ($p<0.001$, 95% CI, -17.9, -8.4)]. This QTc decrease reached a nadir of -32.4 ms ($p<0.001$, 95% CI, -38.4, -26.3) at 1 month post-transplant, and remained shortened at 6 months post-transplant, [mean QTc decrease of 29.4 ms ($p<0.001$, 95% CI, -36.4, -22.4)]. Those with pre-transplant QTc prolongation exhibited a more robust mean QTc shortening at all follow-up time points. Delayed graft function was associated with delayed QTc shortening post-transplant. Three out of four patients who suffered cardiac death within the first year post transplantation had QTc prolongation at the time of transplantation and represented 2.7% of those with pre-transplant QTc prolongation.

Our study demonstrates a rapid and long-lasting QTc interval shortening after successful kidney transplantation. The prompt shortening, coupled with delayed shortening when graft function is delayed, strongly suggests that prolonged QTc in ESRD patients is the consequence of electrolyte disorders and/or accumulated uremic toxins rather than myocardial injury. Three out of four cardiac deaths in the first year post-transplantation occurred in those patients with pre-transplant QTc prolongation.

Keywords: Renal transplant; QTc; Sudden cardiac death; End stage renal disease

Introduction

Cardiovascular disease (CV) is the leading cause of mortality in Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) patients [1]. Sudden Cardiac Death (SCD), the most common cause of cardiac death in ESRD patients, is defined as sudden cessation of cardiac mechanical activity with hemodynamic collapse, often due to sustained ventricular tachycardia or ventricular fibrillation. In the general population above the age of 35, the annual rate of SCD is 0.1%-0.2%, with at least half of these individuals having evidence of Coronary Artery Disease (CAD) on postmortem examination [2]; whereas the annual rate of SCD in ESRD patients is far greater, estimated to be 7% [2]. This increased risk is not due predominantly to CAD [3]. Unlike non-ESRD patients, the risk of SCD in ESRD patients has not been shown to be improved greatly post percutaneous coronary intervention or coronary artery bypass graft, or with improvement of traditional CV risk factors [2-4].

Prolongation of the QT interval, defined as the time from onset of ventricular depolarization to completion of repolarization (or prolonged QT interval corrected for heart rate, [QTc]), is a known risk factor for ventricular arrhythmias, specifically Torsades de Pointes, which can quickly degenerate into ventricular fibrillation and death. Furthermore, a prolonged QTc is considered a significant risk factor for developing arrhythmias in patients receiving hemodialysis [5]. Each 10 ms increase in QTc has been reported to be associated with an 8% increase in mortality in ESRD patients [2].

As early as 1998, studies demonstrated a survival advantage for ESRD patients who underwent cadaveric renal transplant [6]. A systematic review of 110 studies comparing chronic dialysis patients with kidney transplant recipients showed that receiving a kidney transplant was associated with significantly reduced mortality and decreased cardiac events [7]. Successful kidney transplantation confers a significant protection from CV death through unclear mechanisms. While the rate of major Cardiovascular Events (CE) in renal transplant patients is lower than in those patients still on dialysis, it is still higher than the general population. One study noted the incidence of acute coronary syndrome in renal transplant recipients to be 6.5 per 1000 patient-years [8]. The objectives of this study were to examine the changes in the QTc after kidney transplantation, to gain insight into possible mechanisms for the changes observed, and to determine whether an association exists between the occurrence of all cardiac deaths in the first year after transplantation with the QTc pre-transplant or after transplantation.

Methods

Study population and data collection

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A retrospective chart review was performed on all patients who received kidney transplants at Houston Methodist Hospital (Houston, Texas) between 1/1/2014 until 12/31/2015. Conventional machine automated 12-lead Electrocardiograms (EKGs) were used to record QTc. The machine-generated EKG used Bazett's formula ($QTc = QT/\sqrt{RR}$) to correct the QT interval for the patient's heart rate to generate the QTc. All QTc data was recorded on EKGs done 1 day before kidney transplant, and 2 days, 2 weeks, 1 month, 3 months and 6 months post-transplant. Patients were excluded from analysis if they had EKGs with baseline atrial or ventricular tachy-arrhythmias, had EKGs with paced rhythms, had un-interpretable EKGs due to poor baseline waveforms, or had no pre-transplant EKG performed. Patients with prior organ transplants were included in the analysis however those who received simultaneous dual organ transplants (i.e. heart, liver, lung, pancreas along with kidney) were excluded. After applying these exclusion criteria, a total of 309 kidney transplant recipients were included in the study cohort.

Study objectives

The primary objective of the study was to determine whether QTc changed after kidney transplantation. This was determined by comparing the change in QTc between the QTc recorded 1 day before transplant and the QTc recorded at each follow-up time point.

A second objective of this study was to assess QTc changes over the 6 months follow-up, and to assess the direction, rate and magnitude of QTc change. For the first subgroup analysis, transplant recipients were stratified according to the presence or absence of pre-transplant QTc prolongation defined as >450 ms in men and >470 ms in women [9]. As live donor transplant recipients may differ from recipients of deceased donor kidneys in terms of demographic characteristics and post-transplant course in the second subgroup analysis patients were stratified according to whether they received a live *vs* deceased donor kidney. The final subgroup analysis compared QTc changes, and rate of change in those with delayed *vs* prompt graft function. Delayed Graft Function (DGF) was defined as requiring dialysis within the first week after transplantation.

A third objective of the present study was to determine whether any association existed between the pre-transplant QTc, or the QTc at pre-specified time points post-transplant, and cardiac death occurring within the first year post-transplantation. The data reported to the Scientific Registry for Transplant Recipients by the transplant center was reviewed for reported cardiac deaths within that time frame.

Medication regimen

A standard post-transplant medication regimen was used in all patients consisting of Prednisone, Mycophenolic Acid, Tacrolimus, Trimethoprim-Sulfamethoxazole, Fluconazole, Clotrimazole, and Acyclovir.

Statistical analysis

Demographic and baseline (pre-transplant) data were collected from the United Network for Organ Sharing (UNOS) database and the electronic medical records at Houston Methodist Hospital. Values were reported as Median and Interquartile Range (IQR) for continuous variables, and as frequencies and proportions for categorical variables. Missing data were assessed for Missing Completely at Random (MCAR) and Covariate-Dependent Missingness (CDM) using the Little's chi-squared test [10]. Linear mixed models were used to examine the potential risk factors associated with the change of QTc over time. Given the known contribution of electrolyte disturbances to QTc changes, all available potassium, calcium and magnesium values obtained from the electronic medical records at the studied time points were recorded and analyzed in the mixed model as potential risk factors. Post hoc marginal pairwise comparisons were performed to determine the adjusted means (with p-values and 95% CIs) of QTc changes from baseline to 6-months post-transplant. All analyses were performed on Stata version 14.2 (StataCorp LLC, College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

Results

Study population and baseline and follow-up data

Demographic and baseline characteristics for all recipients and for the patients who fell into specified sub-groups are shown in Table 1. Median age was 49 years; 61% were male; 40% were Caucasian; 28% were diabetic.

Serum electrolyte values available pre-transplant and at each follow-up time point, are shown in Supplemental Table 1. There was a substantially smaller number of pre-transplant magnesium values recorded (n=173), compared to potassium (n=309) and calcium (n=309), most likely due to the fact that the frequently ordered Basic Metabolic Profile does not include magnesium. However, this discrepancy diminished with time.

The multivariable linear mixed model suggested that compared to patients with normal pre-transplant QTc, patients having a pre-transplant prolonged QTc were more likely to have a higher mean change in QTc over time after transplantation (23.8 ms, p<0.001). Diabetes and having a higher magnesium level were independently associated with a higher mean change in QTc (7.4 ms, p=0.005; and 6.8 ms, p=0.016, respectively). Conversely, male gender and higher potassium and calcium levels were associated with a shorter post-transplant QTc over time after transplantation (-10.2 ms, p<0.001; -4.6 ms, p<0.001; and -6.1 ms, p<0.001) (Table 2).

At each follow-up time point, there was an increasing number of patients who did not have an EKG documented in the medical chart (Supplemental Table 2). The increasing lack of QTc data upon extended follow-up was adjusted for using the linear mixed model. Using the maximum likelihood estimation, linear mixed model is a powerful tool in dealing with missing values, a common phenomenon in longitudinal studies, in addition to the issue of unbalanced time interval between measurements [11,12]. Additionally, Little's chi-squared test for MCAR and CDM had non-significant p-values (0.15 and 0.89, respectively), which suggest that the missing values could be completely at random and do not influence the outcome.

Primary objective

The median pre-operative QTc in the study population was 450 ms (Table 1). All recipients had a rapid post-transplant QTc shortening as early as 2 days post-transplant with a mean QTc decrease of 13.2 ms (p<0.001, 95% CI -17.9, -8.4) compared to the pre-transplant QTc. The QTc nadir was reached at 1 month post-transplant [mean QTc decrease 32.4 ms (p<0.001, 95% CI -38.4, -26.3)] and the decrease persisted at 6 months post-transplant (29.4 ms [p<0.001, 95% CI -36.4, -22.4]). The mean QTc was seen to decrease by an average of 13.2 ms (p<0.001, 95% CI -17.9, -8.4) 2 days post-transplant, 25.8 ms (p<0.001 95% CI -32.0,-19.5) 2 weeks post-transplant, 32.4 ms (p<0.001 CI -32,-26.3) 1 month post-transplant, 30.6 ms (p-value<0.001 CI -36.8, -24.4) 3 months post-transplant, and 29.4 ms (p-value<0.001 CI -36.4, -22.4) 6 months post-transplant (Supplemental Table 3).

Characteristics	All recipients	Stratified by pre-transplant QTc			Stratified by donor type			Stratified by DGF		
		Non prolonged	Prolonged	p-value	Living	Deceased	p-value	Prompt Graft Function	DGF	p-value
Recipient characteristics										
Recipient n(%)	309 (100)	196 (63.4)	113 (36.6)		144 (46.6)	165 (53.4)		247 (79.9)	62 (20.1)	
Age (years), median (IQR)	48.5 (39.4, 59.0)	48.0 (38.2, 59.0)	49.8 (41.2, 59.1)	0.39	49.0 (39.0, 59.2)	48.0 (40.0, 58.6)	0.71	48.0 (38.3, 58.7)	51.6 (43.0, 60.0)	0.17
Gender				<0.001			0.21			0.83
Female	121 (39.2)	91 (46.4)	30 (26.5)		51 (35.4)	70 (42.4)		96 (38.9)	25 (40.3)	
Male	188 (60.8)	105 (53.6)	83 (73.5)		93 (64.6)	95 (57.6)		151 (61.1)	37 (59.7)	
Race/ethnicity				0.63			<0.001			0.041
White	122 (39.5)	81 (41.3)	41 (36.3)		82 (56.9)	40 (24.2)		103 (41.7)	19 (30.6)	
Black	86 (27.8)	50 (25.5)	36 (31.9)		21 (14.6)	65 (39.4)		60 (24.3)	26 (41.9)	
Hispanic	73 (23.6)	46 (23.5)	27 (23.9)		28 (19.4)	45 (27.3)		62 (25.1)	11 (17.7)	
Others	28 (9.1)	19 (9.7)	9 (8.0)		13 (9.0)	15 (9.1)		22 (8.9)	6 (9.7)	
Race Black				0.23			<0.001			0.006
No	223 (72.2)	146 (74.5)	77 (68.1)		123 (85.4)	100 (60.6)		187 (75.7)	36 (58.1)	
Yes	86 (27.8)	50 (25.5)	36 (31.9)		21 (14.6)	65 (39.4)		60 (24.3)	26 (41.9)	
BMI, median (IQR)	27.8 (23.6, 31.3)	27.4 (23.3, 31.3)	28.2 (24, 31.3)	0.48	27.7 (23.6, 30.8)	27.8 (23.6, 31.4)	0.95	27.3 (23.2, 30.9)	28.8 (25.1, 32.8)	0.019
BMI				0.86			0.59			0.17
Underweight (BMI <18.5)	8 (2.6)	6 (3.1)	2 (1.8)		3 (2.1)	5 (3.0)		7 (2.8)	1 (1.6)	
Normal weight (BMI 18.5-24.9)	102 (33.0)	66 (33.7)	36 (31.9)		46 (31.9)	56 (33.9)		88 (35.6)	14 (22.6)	
Overweight (BMI 25.0-29.9)	98 (31.7)	60 (30.6)	38 (33.6)		51 (35.4)	47 (28.5)		77 (31.2)	21 (33.9)	
Obese (BMI≥30)	101 (32.7)	64 (32.7)	37 (32.7)		44 (30.6)	57 (34.5)		75 (30.4)	26 (41.9)	
Diabetes				0.024			0.43			<0.001
No	223 (72.2)	150 (76.5)	73 (64.6)		107 (74.3)	116 (70.3)		191 (77.3)	32 (51.6)	
Yes	86 (27.8)	46 (23.5)	40 (35.4)		37 (25.7)	49 (29.7)		56 (22.7)	30 (48.4)	
Cold ischemia time (hour, all recipients), median (IQR)	11.2 (1.0-21.7)	8.4 (0.9-21.6)	14.7 (1.3-22.1)	0.021	1.0 (0.8-1.3)	21.3 (16.2-25.8)	<0.001	2.8 (0.9-19.6)	23.0 (13.7-27.7)	<0.001
Cold ischemia time (hour, deceased-donor recipients only), median (IQR)	21.3 (16.2, 25.8)	21.9 (15.8, 25.8)	20.5 (16.4, 25.8)	0.58		21.3 (16.2, 25.8)	<0.001	20.2 (15.1, 24.4)	23.9 (16.9, 27.9)	0.027
Pre-op QTc (ms), median(IQR)	450 (429, 469)	435 (422.5, 448)	474 (464, 490)	<0.001	440 (424, 460)	455 (438, 475)	<0.001	448 (429, 467)	461 (440, 474)	0.011
Pre-op prolonged QTc				<0.001			0.006			0.12

No	196 (63.4)	196 (100.0)	0 (0.0)		103 (71.5)	93 (56.4)		162 (65.6)	34 (54.8)	
Yes	113 (36.6)	0 (0.0)	113 (100.0)		41 (28.5)	72 (43.6)		85 (34.4)	28 (45.2)	
Pre-op Creatinine (mg/dL), median (IQR)	7.8 (5.6, 10.3)	7.6 (5.5, 9.9)	8.8 (6.0, 11.1)	0.021	6.8 (5.3, 9.6)	8.4 (6.1, 11.1)	<0.001	7.5 (5.5, 10.3)	8.0 (6.3, 10.1)	0.26
Pre-op potassium (meq/ L), median (IQR)	4.4 (4.0, 4.8)	4.5 (4.1, 4.8)	4.3 (4.0, 4.8)	0.056	4.4 (4.0, 4.8)	4.4 (4.0, 5.0)	0.41	4.4 (4.0, 4.8)	4.3 (4.0, 5.0)	0.76
Pre-op calcium (mg/dL), median (IQR)	9.2 (8.7, 9.8)	9.4 (8.8, 9.9)	9.0 (8.5, 9.6)	0.002	9.4 (8.8, 9.9)	9.1 (8.7, 9.7)	0.041	9.2 (8.7, 9.8)	9.4 (8.7, 9.7)	0.44
Pre-op magnesium (mg/dL), median (IQR)	2.2 (2.0, 2.4)	2.2 (2.0, 2.4)	2.2 (1.9, 2.4)	0.94	2.0 (1.7, 2.0)	2.2 (2.0, 2.4)	<0.001	2.2 (2.0, 2.5)	2.1 (2.0, 2.4)	0.45
Dialysis type/Pre-emptive				0.008			<0.001			0.003
Pre-emptive Transplant	55 (17.8)	43 (21.9)	12 (10.6)		41 (28.5)	14 (8.5)		53 (21.5)	2 (3.2)	
Peritoneal dialysis (PD)	66 (21.4)	46 (23.5)	20 (17.7)		35 (24.3)	31 (18.8)		52 (21.1)	14 (22.6)	
Hemodialysis (HD)	188 (60.8)	107 (54.6)	81 (71.7)		68 (47.2)	121 (72.7)		142 (57.5)	46 (74.2)	
Days on dialysis (days), median (IQR) (n=254)	1138 (525, 1898)	905 (470, 1627)	1419 (652, 2282)	0.005	507 (361, 923)	1566 (929.5, 2365)	<0.001	919.5 (450, 1680)	1455 (853.5, 2330)	<0.001
Patient status				0.25			0.083			<0.001
Alive	302 (97.7)	193 (98.5)	109 (96.5)		143 (99.3)	159 (96.4)		245 (99.2)	57 (91.9)	
Dead	7 (2.3)	3 (1.5)	4 (3.5)		1 (0.7)	6 (3.6)		2 (0.8)	5 (8.1)	
Graft status				0.95			0.17			<0.001
Functioning	295 (95.5)	187 (95.4)	108 (95.6)		140 (97.2)	155 (93.9)		241 (97.6)	54 (87.1)	
Failure	14 (4.5)	9 (4.6)	5 (4.4)		4 (2.8)	10 (6.1)		6 (2.4)	8 (12.9)	
Delayed graft function				0.12			<0.001			<0.001
No	247 (79.9)	162 (82.7)	85 (75.2)		135 (93.8)	112 (67.9)		247 (100.0)	0 (0.0)	
Yes	62 (20.1)	34 (17.3)	28 (24.8)		9 (6.3)	53 (32.1)		0 (0.0)	62 (100.0)	
Donor characteristics										
Donor age (years), median (IQR)	39.0 (28.0, 49.0)	38.5 (29.0, 49.5)	39.0 (26.0, 49.0)	0.6	43.0 (34.0, 51.5)	36.0 (21.0, 47.0)	<0.001	39.0 (28.0, 49.0)	39.0 (31.0, 49.0)	0.85
Donor type				0.006			<0.001			<0.001
Living	144 (46.6)	103 (52.6)	41 (36.3)		144 (100.0)	0 (0.0)		135 (54.7)	9 (14.5)	

Deceased	165 (53.4)	93 (47.4)	72 (63.7)		0 (0.0)	165 (100.0)		112 (45.3)	53 (85.5)	
Donor eGFR*(ml/min/1.73m2), median (IQR)	106.1 (88.2, 117.7)	105.4 (87.6, 116.8)	108.0 (89.7, 121.9)	0.27	108.2 (99.6, 115.4)	102.8 (65.0, 126.8)	0.012	106.9 (92.9, 117.9)	103.4 (65.0, 116.6)	0.092
Donor BMI, median (IQR)	26.1 (22.9, 29.6)	26.3 (23.2, 29.6)	25.7 (22.5, 28.3)	0.17	25.9 (23.5, 28.2)	26.2 (21.8, 30.7)	0.71	25.9 (22.7, 29.2)	26.7 (23.8, 31.0)	0.086
Donor history of diabetes				0.25						0.77
No	153 (93.3)	84 (91.3)	69 (95.8)			153 (93.3)		104 (93.7)	49 (92.5)	
Yes	11 (6.7)	8 (8.7)	3 (4.2)			11 (6.7)		7 (6.3)	4 (7.5)	
Donor history of hypertension				0.51			<0.001			<0.001
No	272 (88.3)	174 (89.2)	98 (86.7)		141 (97.9)	131 (79.9)		226 (91.9)	46 (74.2)	

Table 1: Demographic and baseline characteristics of all recipients and stratified subgroups.

Note: Values are in number and % unless otherwise specified.
*eGFR=Estimated glomerular filtration rate, calculated using CKD-EPI equation; IQR=Interquartile range; BMI=Body mass index

Variable	Adjusted coefficient (95%CI)*	p
Pre-op prolonged QTc	23.71 (19.17, 28.25)	<0.001
Age	0.10 (-0.07, 0.27)	0.24
Male	-10.26 (-14.74, -5.79)	<0.001
African American	4.43 (-0.35, 9.21)	0.07
Diabetes	7.45 (2.34, 12.57)	0.004
Creatinine	0.58 (-0.09, 1.25)	0.09
Potassium	-4.72 (-7.04, -2.39)	<0.001
Calcium	-6.04 (-7.97, -4.12)	<0.001
Magnesium	5.92 (0.47, 11.37)	0.03
Hemodialysis	4.27 (-0.62, 9.15)	0.09
Years on dialysis	0.12 (-0.59, 0.84)	0.73
Delayed graft function (DGF)	0.77 (-6.25, 7.78)	0.83
Deceased donor	-0.71 (-5.92, 4.51)	0.79

Table 2: Linear mixed model (multivariate), potential risk factors associated with QTc change.

*Adjusted in the multivariate linear mixed model.

Second objective: Subgroup analyses

Normal QTc *vs* prolonged QTc pre-transplant: A prolonged QTc before transplantation was present in 37% of recipients. Compared to those patients with a normal pre-transplant QTc (median QTc=435 ms), patients with prolonged QTc (median QTc=474 ms) were predominantly male (73.5% *vs* 53.6%), diabetic (35.4% *vs* 23.5%), and more often on hemodialysis (71.7% *vs* 54.6%) with longer time on dialysis (1419 *vs* 905 days). In 165 deceased-donor recipients, 72 (43.6%) had prolonged pre-transplant QTc; in contrast only 28.5% of living donor recipients had pre-transplant prolonged QTc (p=0.006).

Transplant recipients with prolonged pre-transplant QTc exhibited a more robust QTc decrease at all follow-up time points as compared to recipients with normal QTc as shown in (Table 3). As in the group with prolonged QTc, consistent with our primary outcome findings, QTc reached a nadir at 1 month and persisted at 6 month post-transplant.

Living donor *vs* deceased donor subgroup: Of the study population, 46.6% received living and 53.4% received deceased donor kidneys. Recipients of deceased donor kidneys were more often black (39.4% *vs* 14.6%, p<0.001), on pre-transplant hemodialysis (i.e. fewer pre-emptive transplants; 72.7% *vs* 47.2%, p<0.001), and had more prolonged median pre-transplant QTc of 455 ms (*vs* 440 ms in recipients of living donor kidneys, p<0.001). Among 254 patients who were on dialysis prior to transplant, recipients of deceased donor kidneys also had a longer time on dialysis compared with recipients of living donors (Table 1).

Recipients of deceased donor kidneys exhibited a more rapid and robust QTc shortening at 2 days post-transplant with mean QTc decrease of 14.6 ms (p<0.001, 95% CI -19.6, -9.5) as compared to recipients of living donor kidneys with a mean QTc decrease of 6.3 ms (p=0.379, 95% CI -20.3, 7.7) as shown in (Table 3). This decrease reflects prolonged pre-transplant QTc in the recipients of cadaveric kidneys.

Prompt graft function *vs*. DGF subgroup: DGF occurred in 20% (62/309) of transplant recipients. Compared to patients with prompt graft function patients with DGF were more often black (42% *vs* 24%), diabetic (48% *vs* 22%), had longer cold ischemia times (this comparison of ischemic times reflects only deceased donor recipients) were more often on hemodialysis (74% *vs* 57%) with longer time on dialysis (1455 *vs* 920 days), received more deceased donor kidneys (86% *vs* 45%), and had more prolonged median pre-transplant QTc of 461 ms (*vs* 448 ms in the prompt graft function group) (Table 1).

Patients with DGF and prompt graft function both exhibited similar reductions in QTc however the prompt graft function group reached their nadir earlier (2 weeks) as compared to the DGF group (1 month) as shown in (Table 3). At 2 weeks post-transplant, patients with prompt graft function exhibited a more robust mean QTc decrease of 28 ms (p<0.001, 95% CI -35.4, -20.6) as compared to patients with DGF who had mean QTc decrease of 15.7 ms (p<0.001, 95% CI -24.4, -7). Also, at 3 months post-transplant, patients with prompt graft function had a more robust mean QTc decrease of 32.9 ms (p<0.001, 95% CI -40.4, -25.5) as compared to patients with DGF who had mean QTc decrease of 21.9 ms (p<0.001, 95% CI -31.1, -12.7).

Third objective: Cardiac death and QTc.

A total of 4 patients suffered cardiac death (all sudden) in the first year post transplantation. The average age of these patients was

Follow-up time point	Non-prolonged pre-op QTc (N=196)		Prolonged pre-op QTc (N=113)	
	Mean (ms) (95% CI)	p	Mean (ms) (95% CI)	p
2 days, post-transplant	-6.5 (-12.4, -0.6)	0.03	-22.4 (-28.8, -16.1)	<0.001
2 weeks, post-transplant	-16.3 (-23.3, -9.2)	<0.001	-39.1 (-47.2, -31.1)	<0.001
1 month, post-transplant	-23.3 (-30.2, -16.4)	<0.001	-45.1 (-52.9, -37.2)	<0.001
3 months, post-transplant	-21.7 (-28.8, -14.6)	<0.001	-43.1 (-51.1, -35.1)	<0.001
6 months, post-transplant	-18.4 (-26.7, -10.2)	<0.001	-44.7 (-54.4, -35.0)	<0.001
Follow-up time point	**Living donor (N=144)**		**Deceased donor (N=165)**	
	Mean (ms)	**p**	**Mean (ms)**	**p**
2 days, post-transplant	-6.3 (-20.3, 7.7)	0.38	-14.6 (-19.6, -9.5)	<0.001
2 weeks, post-transplant	-22.1 (-36.4, -7.8)	0.003	-23.5 (-30.5, -16.5)	<0.001
1 month, post-transplant	-25.0 (-39.4, -10.7)	0.001	-32.6 (-39.5, -25.7)	<0.001
3 months, post-transplant	-28.7 (-43.3, -14.2)	<0.001	-28.1 (-35.2, -21.0)	<0.001
6 months, post-transplant	-25.7 (-41.7, -9.7)	0.002	-27.9 (-36.1, -19.6)	<0.001
Follow-up time point	**Prompt Graft Function (N=247)**		**DGF* (N=62)**	
	Mean (ms)	**p**	**Mean (ms)**	**p**
2 days, post-transplant	-12.7 (-18.8, -6.5)	<0.001	-14.5 (-21.4, -7.6)	<0.001
2 weeks, post-transplant	-28.0 (-35.4, -20.6)	<0.001	-15.7 (-24.4, -7.0)	<0.001
1 month, post-transplant	-31.2 (-38.4, -24.0)	<0.001	-33.6 (-42.7, -24.5)	<0.001
3 months, post-transplant	-32.9 (-40.4, -25.5)	<0.001	-21.9 (-31.1, -12.7)	<0.001
6 months, post-transplant	-29.6 (-38.2, -21.0)	<0.001	-25.8 (-36.9, -14.8)	<0.001

Table 3: Mean change over time of QTc in comparison with pre-op QTc for subgroup analyses.

*DGF=Delayed graft function; ms=Millisecond

From baseline to 6 months, patients with prolonged pre-op QTc shortened their QTc 21.9 ms faster than patients with non-prolonged pre-op QTc which was statistically significant (p<0.001, 95% CI 17.3, 26.5). From baseline to 6 months, multivariate analysis suggested no statistically significant difference in the mean change of QTc between patients who received deceased donor kidneys versus living donor kidneys (p=0.749) and between patients with delayed graft function versus without delayed graft function (p=0.133).

58 years. All of these patients had been dialysis dependent prior to transplant (three on hemodialysis, one on peritoneal dialysis). These patent averaged 2759.5 days on dialysis prior to transplantation. All these patients were male, and three out of four had DGF. The average number of days from transplant to time of cardiac death was 104 days. The average pre-transplant QTc in this group was 466.25 ms. While three out of four had a prolonged pre-transplant QTc, only one of the four deaths had a prolonged QTc at the time most proximate to the date of death while the others improved.

Discussion

Prolongation of the QTc interval in patients with end stage renal disease undergoing dialysis is correlated with increased risk of cardiovascular death. The purpose of the present study was to investigate changes in the QTc interval following renal transplantation. The study data demonstrate a lasting shortening in the QTc interval following kidney transplantation. This observation of QTc shortening post-kidney transplant is consistent with another small study by Monfared, et al. in which the QTc from 26 kidney allograft recipients was compared to the QTc of 26 patients who were on hemodialysis [13]. The post-transplanted patients had an average maximum QTc of 436.3 ± 19 ms, while the hemodialysis patients had an average maximum QTc of 464.7 ± 23 ms. The difference in these two cohorts was thought to be due to normalization of electrolytes and acid base status [13].

In the present study, one interesting result on multivariate analysis was the relationship between magnesium and QTc change. Traditionally, hypokalemia, hypocalcemia, and hypomagnesemia have all have been associated with prolongation of QTc. Our model showed that hypokalemia and hypocalcemia were both indeed associated with prolonging post-transplant QTc; however, hypomagnesemia appeared to be associated with shortened post-transplant QTc. The p value for the magnesium-QTc association was less robust when compared to the other 2 electrolytes, but remained statistically significant. It is unclear if we can draw any definitive conclusions about this association due to the large number of missing magnesium values recorded in the pre-transplant time point. Of interest however is the observation that despite our patients being started on multiple potentially QTc-prolonging medications (i.e. tacrolimus, trimethoprim-sulfamethoxazole, famotidine, azoles, etc) after transplant, the QTc still shortened at all follow-up time points. Tacrolimus is known to cause hypomagnesemia through renal magnesium wasting, and a prior study by Navaneethan et al. demonstrated that serum magnesium levels correlated inversely with tacrolimus concentrations and creatinine clearance [14]. Despite hypomagnesemia, a known consequence of tacrolimus therapy, shortening of the QTc occurred post-transplant nevertheless.

Of note QTc shortening was more robust in the deceased donor *vs* living donor recipients at 2 days post-transplant. This is likely a consequence of statistically and clinically significantly higher pre-transplant QTc in the recipients of deceased donor kidneys (455 ms *vs.* 440 ms in recipients of living donor kidneys), reflecting their longer time on dialysis. Consistent with the prior subgroup analysis, patients starting with a prolonged pre-transplant QTc appear to benefit more in terms of rapidity and degree of QTc shortening as compared to patients that started with a normal pre-transplant QTc.

The observation that in the DGF *vs* prompt recovery subgroup (no DGF), the finding of QTc shortening being more robust in the no DGF group at 2 weeks and 3 months post-transplant is informative. These findings highlight the importance of graft function on QTc changes post-transplant. This along with the rapidity of shortening of the QTc after transplantation (2 days) suggests an important role for

Event	Age	Days on dialysis	Modality	Days after transplant event occurred	DGF	Gender	Pre-transplant QTc (ms)	QTc 2 days post-transplant	QTc 2 weeks post-transplant	QTc 1 month post-transplant	QTc 3 month post-transplant
SCD	65	809	HD	162	Yes	M	424	417	405	382	445
SCD	49	5725	HD	221	Yes	M	477	457	425	-----	404
SCD	57	2098	PD	6	Yes	M	513	478	-----	-----	-----
SCD	64	2406	HD	30	No	M	451	445	429	-----	-----

Table 4: Demographics and QTc values of patients with Cardiac Death within 1 year of transplant.

Abbreviations: PD: Peritoneal Dialysis, HD: Hemodialysis, DGF: Delayed Graft Function, POD: Post-operative Day

uremic toxins and fluid and electrolyte alterations in the pathogenesis of prolonged QTc in patient with ESRD undergoing dialysis.

Since prolonged QTc is strongly associated with cardiovascular death in patients undergoing dialysis, one objective of the present study was to determine whether recipients who succumb to cardiac death in the first year post-transplantation had prolonged pre-transplant QTc or persistent QTc prolongation post-transplantation. Only four sudden cardiac deaths occurred in this cohort within the first year post transplantation. This represents an incidence of 1.29%, ten-fold the incidence of SCD in the general population (0.1%-0.2%). This still contrasts dramatically to the annual incidence of sudden cardiac death in dialysis patients, which is approximately 7% [3]. Therefore, it can be concluded that normalization of the QTc interval after transplantation is associated with a substantial decrease in sudden cardiac death in the first year post kidney transplantation (Table 4). Of interest, three out of four of the patients succumbing to cardiac death had a prolonged QTc pre-transplantation, and in one the QTc remained prolonged proximate to the date of death. Those patients who suffered cardiac death represented 2.7% of transplant recipients with prolonged QTc at the time of transplantation. Also three of the four decreased patients had DGF. Therefore patients with prolonged QTc undergoing kidney transplantation should be considered at higher risk of cardiac death in the first year after transplantation, a risk potentially magnified by DGF.

The strengths of this study include: protocol based post-transplant pharmacologic regimens (which reduce the impact of medication differences), and the large sample size with up to 6 months of follow-up data. This lends credence to the observed durability of post-transplant QTc shortening, which may explain in part the cardiovascular protection that transplant affords to ESRD patients.

Study limitations include missing data with time after transplantation and use of automated QTc generation. However, the linear mixed model used in our study has been shown to be flexible and good for handling any degree of imbalance in the data [9]. In addition all EKGs were reviewed by a physician and those demonstrating arrhythmias, paced-rhythm or poor baseline waveforms were excluded from analysis.

Conclusion

This study demonstrates that there is a rapid, substantial and durable QTc shortening in patients post kidney transplant. The mechanisms for this are unclear but appear to be related to normalization of the body's milieu consonant with improvement of renal function. The normalization of QTc following kidney transplantation appears to be associated with a marked reduction in the incidence of sudden cardiac events and three out of the four cardiac events in the first year post transplantation occurred in individuals with prolonged QTc at the time of transplantation.

Disclosures

No disclosure.

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