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Risk Assessment for Arrhythmia in Pediatric Renal Transplant Recipients

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Abstract

Objectives: **Renal transplant recipients are at risk for ventricular arrhythmia and sudden death. To assess that risk, we compared the ventricular repolarization markers of pediatric renal transplant recipients with those of healthy children.**

Materials and Methods: **We included 30 children and adolescents who were followed for at least 6 months after renal transplant; 30 age- and sex-matched children were included for the control group. Demographic features, medications, and laboratory findings were recorded. Blood pressure measurements, ventricular repolarization indexes including QT dispersion, corrected QT dispersion, T-wave peak-to-end interval dispersion, the T-wave peak-to-end interval/QT ratio, the T-wave peak-to-end interval/corrected QT ratio, left ventricular mass index, and relative wall thickness were compared between groups. In addition, the correlations of ventricular repolarization indexes with other variables were evaluated.**

Results: **Blood pressure standard deviation scores, the mean heart rate, QT dispersion, corrected QT dispersion, the T-wave peak-to-end interval/QT ratio, the T-wave peak-to-end interval/corrected QT ratio, left ventricular mass index, and relative wall thickness values were significantly higher in renal transplant patients, whereas T-wave peak-to-end interval dispersion, ejection fraction, and fractional shortening were similar between groups. Although ventricular repolarization indexes were similar in patients with and without left ventricular hypertrophy, only corrected QT dispersion was significantly higher in patients with hypertension ($P = .006$). The only variable that significantly predicted prolonged corrected QT dispersion was the systolic blood pressure standard deviation score ($P = .005$, $\beta = .403$).**

Conclusions: **Ventricular repolarization anomalies, hypertension, left ventricular hypertrophy, and cardiac geometry irregularity may be observed after renal transplant in pediatric recipients despite acceptable allograft functions and normal serum electrolyte levels. Control of systolic blood pressure would decrease the risk of ventricular repolarization abnormalities, namely, the corrected QT dispersion. Follow-up of cardiovascular risks with noninvasive methods is recommended in all pediatric renal transplant recipients.**

Key words: *Ventricular repolarization, Blood pressure, Children*

Introduction

Patients with end-stage renal disease (ESRD) have increased risk for cardiovascular problems, including left ventricular hypertrophy (LVH), systolic and diastolic dysfunction, and ventricular arrhythmia, which may lead to unexpected and sudden death.[1-4] In pediatric renal transplant (RTx) recipients, cardiovascular-related mortality is 100 times higher than in the age-matched population.[5] In a huge group of young RTx recipients, including 18 911 patients who received transplants at < 21 years old, it was demonstrated that the highest cause of death was cardiovascular problems, although cardiovascular mortality rates fell by 16% for every 1 year after RTx.[6] As a result, despite a significant reduction in cardiovascular risk factors such as hypertension, hyperparathyroidism, anemia, and hyperlipidemia, the incidence of cardiac

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mortality has remained high in pediatric RTx recipients.[5,6]

Ventricular repolarization (VR) indexes determined by electrocardiography (ECG) have long been used for determination of the risk of arrhythmia in patients with chronic kidney diseases. Of those, QT interval, QT dispersion (QTd), corrected QT (QTc), and QTc dispersion (QTcd) are indicators of general abnormality of VR and distribution of ventricular recovery time.[1] The T-wave peak-to-end interval (Tp-e) and its dispersion (Tp-ed) are some other indexes of VR. The Tp-e interval provides an index of the maximum dispersion of VR, whereas the Tp-ed value reflects variation of the transmural dispersion of the repolarization vector among different parts of the ventricle.[7,8] Recently, Tp-e/QT and Tp-e/QTc ratios have emerged as novel markers for total variability in the myocardial repolarization that are used as an index of arrhythmogenesis.[8-10] It was assumed that these ratios were more sensitive than Tp-e and QT intervals, since these measurements are not affected by heart rate (HR) and body weight.[11]

Alterations of VR that might contribute to cardiac mortality have been studied in children and adults with RTx.[1-3,12-16] However, to the best of our knowledge, Tp-e/QT and Tp-e/QTc ratios have not been studied before. We conducted this study to determine whether pediatric RTx recipients have higher VR indexes, including QTd, QTcd, Tp-e interval, Tp-e/QT, and Tp-e/QTc as the most sensitive VR indexes, in addition to ejection fraction (EF) and fractional shortening (FS) for left ventricular systolic function, left ventricular mass index (LVMI), and relative wall thickness (RWT) for LVH in our post-RTx population and compared the data with those of healthy children.

Materials and Methods

The study protocol was approved by the institutional review board (08.08.2019/322). Thirty children and adolescents with stable renal function who had follow-up of at least 6 months after RTx between March 2005 and October 2018 were included in the study. Patients were excluded if they were on any medication disruptive to QT duration or if they had heart failure, diabetes mellitus, or a previous history of dysrhythmia or electrolyte imbalances causing QT prolongation (hypokalemia, hypocalcemia, and hypomagnesemia). Patients with low glomerular filtration rate (< 60 mL/min/1.73 m^2) were also excluded. The control group consisted of age- and sex-matched 10- to 18-year-old healthy children (n = 30) who were evaluated in the pediatric cardiology clinic for cardiac murmur and found to have physiological murmur without underlying cardiac pathology.

This was a retrospective study. In our clinic, the standard policy was to evaluate all RTx patients with ECG and echocardiography (ECHO) for cardiac functions at least annually. Demographic features, medications, complete blood count and biochemical values, and estimated glomerular filtration rate (calculated according to the Schwartz formula) at the last visit were recorded, in addition to the last ECG and ECHO findings. Blood pressure (BP) readings recorded in the last 3 visits were averaged in all cases. Standard deviation scores (SDS) for body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) and systolic and diastolic BP (SBP and DBP, respectively) were determined with the online Child Metrics program from the Turkish Pediatric Endocrinology and Diabetes Society.[17] Systolic and/or diastolic blood pressure values of ≥ 95th percentile for age, sex, and height were considered as hypertension. Electrocardiographic and ECHO examinations were performed for all participants.

Electrocardiographic indicators

A standard 12-lead ECG (Cardiofax GEM, model 9022 K; Nihon Kohden) was recorded at a speed of 25 mm/s and an amplitude of 1 mV/cm. Calculations for QT interval, QTd, QTcd, Tp-ed, and Tp-e/QT and Tp-e/QTc ratios were performed for each participant by the same researcher (ES).

QT dispersion.

We measured the QT interval from the beginning of the QRS complex to the end of the T wave. The QTd was calculated as the difference between the maximum and minimum QT intervals. The QT interval corrected for HR was calculated according to the Bazett[18] formula, where QTc is the QT interval divided by the square root of the R-R interval. The QTcd was calculated as the difference between the maximum and minimum of QTc intervals.

Peak-to-end T-wave interval.

The Tp-e was measured from the highest point to the end point of the T wave. If reverse T waves were

present, then the measurement was taken from the lowest point to the end point of the T wave. The Tp-ed is the difference of the maximum and minimum Tp-e.

Echocardiographic examinations

The evaluated parameters were EF and FS obtained by ECHO examination and the calculated LVMI and cardiac geometry parameters. The LVM was calculated with the Devereux formula as follows: 0.8 × {1.04 × ([LVIDed + PWTd + IVSTd]^3 – [LVIDed]^3) + 0.6 g}, where LVIDed is left ventricular internal diameter at the end of diastole, PWTd is posterior wall thickness in diastole, and IVSTd is interventricular septum thickness (in diastole) and indexed to height (in $m^{2.7}$) for LVMI.[19,20] A value of LVMI exceeding the 95th percentile for sex and age in normal children and adolescents was used to define LVH.[20] The RWT was calculated by the following formula: RWT = 2 × PWTd/LVIDed. In patients with LVH, a value of RWT ≤ 0.42 was defined as "eccentric" and > 0.42 was considered "concentric" in terms of cardiac geometry.[21]

Statistical analyses

The SPSS package program (version 24.0) was used for statistical analyses. Continuous variables are shown as mean values ± SD, and descriptive statistics are expressed as frequency. Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables between groups. Normally distributed continuous variables were compared by *t* test, whereas parameters not distributed normally were evaluated by Mann-Whitney U test. The chi-square test was used to compare categorical variables between groups. Depending on the distribution type of the variables, a Pearson or Spearman correlation analysis was performed for bivariate analysis and linear regression for multivariate analysis. $P < .05$ was considered statistically significant for all statistical evaluations.

Results

Thirty RTx recipients and 30 healthy age- and sex-matched children (11 females and 19 males in each group with mean age of 14.3 ± 4.2 years) were included (Table 1). None of the patients in the control group was obese, and the BMI values were similar between the groups ($P < .05$; Table 1). The mean duration after RTx was 54.0 ± 37.9 months in RTx patients. Congenital urological abnormalities (46.6%) were the most common causes of ESRD in these patients, followed by glomerulonephritis (20%), cystic renal diseases (16.6%), chronic tubulopathy (10%), amyloidosis (3.3%), and hemolytic uremic syndrome (3.3%). The mean duration of dialysis in patients receiving hemodialysis or peritoneal dialysis before transplant was 23.2 ± 19.1 months. Twenty-nine patients received mycophenolate sodium and tacrolimus, and 1 patient received mycophenolate sodium and everolimus in addition to corticosteroids for the immunosuppressive therapy. Twenty-one patients were not receiving any antihypertensive therapy. Five patients were using 1 antihypertensive agent, and 4 patients were taking 2 antihypertensive agents. No patient was receiving any other medication known to be associated with QT prolongation. The mean glomerular filtration rate of patients was 102.5 ± 31.3 mL/min/1.73 m^2. Any abnormalities of serum hemoglobin or electrolytes that may cause arrhythmia were absent in participants. The data pertaining to the pediatric RTx recipients are presented in Table 2.

Table 1. Comparison of Blood Pressure Measurements and Electrocardiographic and Echocardiographic Data of Pediatric Renal Transplant Patients and Volunteer Control Patients

	RTx Patients (n = 30)	Control Patients (n = 30)	*P*
Age, y	14.3 ± 4.2	14.3 ± 4.2	1.000
No. of female/male patients	11/19	11/19	1.000
BMI-SDS	-0.10 ± 1.26	-0.22 ± 1.14	.719
SBP-SDS	1.21 ± 1.10	0.54 ± 0.81	.009
DBP-SDS	1.00 ± 1.04	0.04 ± 0.94	.001
HR, beats/min	93.8 ± 17.6	82.3 ± 11.2	.004
QTd	0.04 ± 0.01	0.03 ± 0.02	.001
QTcd	0.05 ± 0.02	0.02 ± 0.02	.001
Tp-ed	0.04 ± 0.03	0.03 ± 0.01	.126
Tp-e/QT	0.17 ± 0.02	0.14 ± 0.036	.003
Tp-e/QTc	0.15 ± 0.01	0.12 ± 0.027	.001
EF, %	67.3 ± 5.4	68.5 ± 5.8	.432
FS, %	37.4 ± 2.96	37.69 ± 4.07	.838
LVMI, g/$m^{2.7}$	38.93 ± 12.95	30.91 ± 8.0	.004
RWT	0.46 ± 0.12	0.40 ± 0.06	.007

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DBP, diastolic blood pressure; EF, ejection fraction; FS, fractional shortening; HR, heart rate; LVMI, left ventricular mass index; QTd, QT dispersion; QTcd, corrected QTd; RTx, renal transplant; RWT, relative wall thickness; SBP, systolic blood pressure; SDS, standard deviation score; Tp-e, T-wave peak-to-end interval; Tp-ed, Tp-e dispersion

Data are mean values ± standard deviation.

Blood pressure measurements

Mean SBP measurements were similar between the groups (119.8 ± 12.4 vs 114.5 ± 10.4 mmHg; $P = .083$), although DBP measurements were significantly higher

in RTx patients (74.0 ± 12.7 vs 65.1 ± 9.4 mmHg; $P = .003$). When we compared SDS values of SBP and DBP measurements, these were both significantly higher in RTx patients (Table 1). None of the patients in the control group was hypertensive, but 40% of the RTx recipients were hypertensive.

Table 2. Demographic Data and Laboratory Parameters of Renal Transplant Patients

Parameter	Result (No. of Patients or Mean ± SD)
Etiology of CKD	
CAKUT	14
Chronic glomerulonephritis	6
Renal cystic disease	5
Chronic tubulopathy	3
Amyloidosis	1
HUS	1
Duration of dialysis, mo (range)	23.2 ± 19.1 (0-84)
Duration of RTx, mo (range)	54.0 ± 37.9 (9-150)
Donor type, n	
Deceased	16
1st degree living related	10
2nd degree living related	2
3rd degree living related	1
4th degree living related	1
Immunosuppressive treatment	
CS+MPS+TAC	29
CS+MPS+mTOR	1
Antihypertensive treatment	
None	21
Yes (with 1 drug/with 2 drugs)	9 (5/4)
eGFR, mL/min/1.73m^2 (range)	102.5 ± 31.3 (61.25-163.8)
Hemoglobin, g/dL (range)	12.5 ± 1.2 (9.6-14.9)
Sodium, mg/dL (range)	140.4 ± 2.0 (136-145)
Potassium, mg/dL (range)	4.3 ± 0.5 (3.4-5.6)
Calcium, mg/dL (range)	10.0 ± 0.5 (8.7-10.8)
Phosphorus, mg/dL (range)	4.1 ± 0.7 (1.6-5.6)

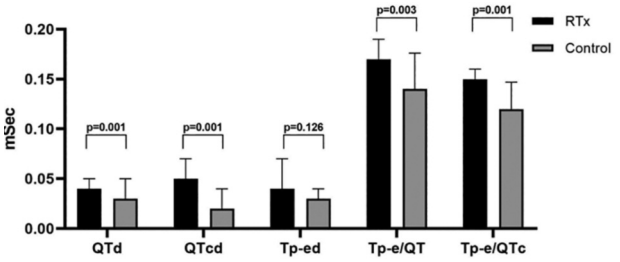
Abbreviations: CAKUT, congenital anomalies of kidney and urinary tract; CKD, chronic kidney disease; CS, corticosteroids; eGFR, estimated glomerular filtration rate; HUS, hemolytic-uremic syndrome; MPS, mycophenolate sodium; mTOR, mammalian target of rapamycin; RTx, renal transplant; SD, standard deviation; TAC, tacrolimus

Electrocardiographic findings

In ECG investigations, mean HR was significantly higher in RTx patients ($P = .004$). The mean QTd and QTcd values were significantly longer in RTx patients ($P = .001$ and $P = .001$, respectively). Although RTx recipients had Tp-e dispersion (Tp-ed) values similar to healthy children, mean Tp-e/QT and Tp-e/QTc ratios were significantly higher than those of the healthy children ($P = .003$; $P = .001$) (Figure 1).

In addition, patients with LVH had similar QTd, QTcd, Tp-ed, Tp-e/QT, and Tp-e/QTc values compared with patients without LVH. In hypertensive cases, only QTcd levels were significantly higher (0.054 ± 0.028 vs 0.035 ± 0.025; $P = .006$), and the other 4 indexes were similar to those of the patients without hypertension.

Figure 1. Comparison of Electrocardiographic Ventricular Repolarization Indexes Between the Groups



Abbreviations: QTc, corrected QT; QTcd, corrected QTd; QTc-max, maximum corrected QT; QTd, QT dispersion; RTx, renal transplant; Tp-e, T-wave peak-to-end interval

Echocardiographic findings

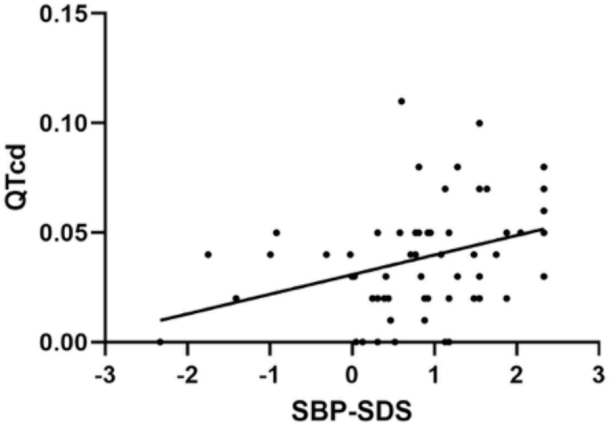
Echocardiographic assessment showed no significant difference in mean EF or FS values between RTx recipients and healthy children ($P > .05$), whereas LVMI and RWT were significantly higher in RTx recipients ($P = .004$ and $P = .007$, respectively; Table 2). The rate of LVH was 47% and those with concentric changes were 37% in RTx recipients.

Correlation analyses

Interestingly, there was no significant correlation between LVMI and SBP-SDS or DBP-SDS. In addition, LVMI was not correlated with QTd, QTcd, Tp-ed, Tp-e/QT, Tp-e/QTc, EF, or FS, but significantly correlated with RWT ($P < .001$, $r = 0.499$) and BMI-SDS ($P = .026$, $r = 0.290$) as expected in univariate analysis. The significance of correlations persisted when adjusted for age, sex, and HR. Multivariate regression analyses showed that only RWT retained significance ($P = .001$, $\beta = .530$).

Time after RTx had no correlation between any ECG or ECHO indicators ($P > .05$). Comparison of the other ECG parameters with the parameters including BMI-SDS, SBP-SDS, DBP-SDS, HR, EF, FS, LVMI, and RWT showed the following correlations. QTcd was significantly correlated with SBP-SDS ($P = .004$, $r = 0.363$), DBP-SDS ($P = .008$, $r = 0.343$), and HR ($P = .008$, $r = 0.341$); Tp-e/QTc was significantly correlated with HR ($P < .001$, $r = -0.491$). The correlation between Tp-e/QTc and HR was no more significant when adjusted for age, sex, and BMI ($P = .165$, $\beta = -.211$). When multivariate analyses were carried out, the only variable significantly predictive of prolonged QTcd was SBP-SDS ($P = .005$, $\beta = .403$) (Figure 2).

Figure 2. Correlation of Corrected QT Dispersion and Systolic Blood Pressure Standard Deviation Score in Pediatric Renal Transplant Recipients



Abbreviations: QTcd, corrected QT dispersion; SBP-SDS, systolic blood pressure standard deviation score

Discussion

We demonstrated that the relatively more sensitive ECG indexes for VR (QTd, QTcd, Tp-e/QT, Tp-e/QTc, BP, LVMI, and RWT) in pediatric RTx recipients were significantly higher than those of healthy control patients. Ventricular indexes were not influenced by LVMI. The QTcd was prolonged in pediatric RTx recipients, and higher SBP-SDS values predicted longer QTcd levels.

Because the most frequent cause of death in pediatric RTx recipients is cardiovascular problems resulting in arrythmia and sudden death, noninvasive prediction methods such as ECG and ECHO are important.[1] Measurement of the QT interval is a noninvasive method for VR assessment.[1,22] Prolonged QT, QTc interval, and QTd have been associated with electrical instability of the myocardium and increased risk for ventricular arrhythmias.[23,24] Recent studies have suggested that QT, QTd, QTc, and QTcd are good predictors for cardiac events just like EF, HR, and HR variability.[2,23-25] Patients with ESRD have shown prolonged QTd and QTcd compared with healthy control patients.[1,13,15,26,27]

The effects of RTx on QT, QTd, QTc, and QTcd were studied previously in several adult and pediatric cohorts (Table 3); in adult RTx recipients, these indexes or only maximum QTc levels significantly improved after RTx, along with improvement in LVMI and serum electrolytes and acid-base status.[2,12-15] There are few pediatric case studies, and the results are conflicting. In the earliest study, QTc levels were in normal ranges and no patient had LVH.[16] In another study, QTc and QTcd levels decreased after RTx and were similar to those of the control group; however, LVMI values were significantly higher in post-RTx patients than in the control patients but regressed remarkably compared with the pretransplant period.[3] In the most recent study, Tp-ed, a relatively novel ECG marker, was evaluated in addition to QTd and QTcd. All VR indexes improved after RTx, although these remained longer than in the control patients,[1] and LVMI was not evaluated. In our study, we evaluated Tp-e/QT and Tp-e/QTc ratios along with QTd, QTcd, and Tp-ed. We demonstrated that, although mean Tp-ed values were similar to healthy individuals, Tp-e/QT and Tp-e/QTc ratios were significantly higher in pediatric RTx recipients in addition to QTd and QTcd, which suggested that these patients were at risk for ventricular arrhythmias. To our knowledge, our study is the first to determine the Tp-ed, Tp-e/QT, and Tp-e/QTc as VR markers in RTx recipients.

Hypertension constitutes a common problem in RTx recipients. Although the underlying mechanisms for the persistence of hypertension after successful RTx is not completely understood, use of high-dose steroids and other immunosuppressive drugs has been reported as a possible contributing factor.[28] Blood pressure SDS values were significantly higher in our patients with RTx compared with the control group. Regression in LVMI is a desired finding after RTx; however, studies in children have conflicting results. In several studies, LVMI and LVH rates and/or cardiac geometry remained similar in the post-RTx period compared with the pre-RTx period or remained significantly higher compared with the control values, although these decreased, especially in the early period.[3,29-31] In the long-term, improvement in LVH has been reported in pediatric renal RTx recipients, and, because the ratio of hypertension increased, no significant correlations between LVMI and BP measurements have been found.[32] In our study, we could not demonstrate a correlation between LVMI and the BP measurements or BP-SDS values, either. However, BP-SDS, LVMI, and RWT levels were significantly higher in RTx patients than those shown in the healthy children. On the contrary, other left ventricular function parameters, including EF and FS, were similar to those shown in the healthy children. These findings suggested that RTx patients do not have normal cardiovascular risk after RTx.

Table 3. Previous Studies on Ventricular Repolarization in Renal Transplant Recipients

Study	Study Group (No.)	ECG Param	ECHO Param	LVMI ~ ECG	Improvement After RTx	Result
				Adults		
Yildiz et al (2001)[12]	HD: RTx (27), control (24)	QTmax, QTmin, QTd	IVSTd, LVPWTd, E/A, LVMI	Present	Improvement in QTd in post-RTx vs pre-RTx (HD) period.	HD patients had abnormal late potentials, which disappeared after RTx.
Koc et al (2002)[13]	RTx (34), control (34)	QTd, QTcd	LVMI	Absent	No pre-RTx group.	RTx patients had similar QTd and QTcd vs control.
Arnol et al (2008)[14]	RTx eGFR ≥ 60 (40), RTx eGFR < 60 (28)	QT, QTc, SDNN-QT, rMSSD-QT, QTRR	IVSTd, LVPWTd, LVIDed, LVMI, E/A, EF	Present	No pre-RTx group.	Greater LVM is associated with increased VR heterogeneity heterogeneity and associated risk of arrhythmia and cardiac death specifically in patients with DGF.
Monfared and Ghods (2008)[2]	RTx (26), HD (26), control (22)	QTc-max, QTd, QTcd	None	ND	Improvement in QTc max of RTx vs HD patients.	Decreased QTc-max levels may result from normalization of electrolytes and acid-base status.
Monfared et al (2012)[15]	Pre-HD to HD: RTx (34)	QTc-max, QTd, QTcd	None	ND	Improvement of QTc-max of RTx patients vs pre-HD and HD period.	Decreased QTc-max levels may result from normalization of electrolytes and uremic status.
				Children		
Butani et al (2002)[16]	CKD (20), RTx (16)	QTc	LVD, LVH, FS	Absent	ND	QTc prolongation is uncommon in children with CKD or RTx in absence of cardiac dilatation.
Kim et al (2009)[3]	RTx (32), control (29)	QTc, QTcd	EF, FS, E/A, LVPGLS, deceleration time, IVRT, Tei index, LVMI	ND	Improvement of QTc and QTcd in RTx patients vs pre-RTx period.	Indexes of VR and LVMI improved; LVMI was significantly higher in RTx vs control.
Amoozgar et al (2013)[1]	RTx (45), control (45)	QTd, QTc, QTcd, Tp-e	EF, FS, IVSTs/d, LVPWTs/d, E/A	ND	QTd, QTcd, and Tp-e improved after RTx.	Indexes of VR improve after RTx, but remain longer vs control.
Our study	RTx (30), control (30)	QTd, QTcd, Tp-e, Tp-e/QT, Tp-e/QTc	EF, FS, LVMI, RWT	Absent	No pre-RTx group.	QTd, QTcd, Tp-e/QT, Tp-e/QTc, LVMI, RWT, and BP were higher in pediatric RTx vs control.

Abbreviations: DGF, decreased graft function; ECG, electrocardiography; ECHO, echocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FS, fractional shortening; HD, hemodialysis; IVRT, isovolumic relaxation time; IVSTs/d, interventricular septum thickness at systole and diastole, respectively; LVD, left ventricular dilatation; LVH, LV hypertrophy; LVIDed, LV internal diameter at the end of diastole; LVMI, LV mass index; LVMI ~ ECG, significant correlation between LVMI and ECG parameters; LVPGLS, LV peak global longitudinal strain; LVPWTs/d, LV posterior wall thickness at systole and diastole, respectively; ND, not determined; Param, parameter; QTcd, corrected QTd; QTc-max, maximum corrected QT; QTd, QT dispersion; QTmax, maximum QT; QTmin, minimum QT; QTRR, QT interval variability relative to heart rate variability; rMSSD-QT, root-mean-square of the successive QT interval difference; RTx, renal transplant; RWT, relative wall thickness; SD, standard deviation; SDNN-QT, SD of normal-to-normal intervals from which artifacts have been removed; Tp-e, T-wave peak-to-end interval

Note: the E/A ratio is a marker of the function of the left ventricle of the heart. E/A represents the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave).

The mechanisms behind repolarization abnormalities are not well defined. Systemic hypertension and LVH have been reported as important factors for QT interval variability and risk of ventricular arrhythmia.[14,33] Reports have shown LVMI to be significantly correlated with VR indexes in several adult studies,[12,14] whereas another study showed that neither BP nor LVMI was related to increased QTd.[13] In children, this association has not been evaluated in previous studies, but it was found that QTd, QTcd, and Tp-e were significantly correlated with left IVSTd1 (Table 3). We could not demonstrate such a correlation between LVMI and VR indexes, but QTcd was significantly correlated with SBP-SDS. In our study, it seems that VR abnormality was likely associated with BP rather than LVMI.

Although this study provides new information on VR abnormalities in RTx recipients, the results should be interpreted within the context of its limitations. First, it was a retrospective study with a small sample size. Although the mean follow-up period of the patients was 52 months, the follow-up periods and the ECG and ECHO schedules for each patient were different. In addition, treatment with tacrolimus could have interfered with the VR indexes. Among the immunosuppressives used after RTx, mostly tacrolimus has been suspected as a cause for prolonged QT levels or various arrhythmogenic phenomena.[33-36] All but one of our patients were on tacrolimus treatment during the study period. Finally, if we had the chance to compare the data of the pretransplant period, this would be a more comprehensive study.

In conclusion, we demonstrated that VR anomalies, hypertension, LVH, and cardiac geometry irregularity may be observed after RTx in pediatric recipients despite acceptable allograft functions and normal serum electrolyte levels. Systolic BP-SDS values were significantly predictive of prolonged QTcd in our study and suggested that control of SBP would decrease the risk of VP abnormalities. We recommend follow-up for cardiac functions, LVH with LVMI and RWT, and VR abnormalities with noninvasive and easily accessible methods, as well as BP measurements in all pediatric RTx recipients. Further studies are needed to resolve the conflicting results in the current literature.

References

1. Amoozgar H, Tavakoli A, Fallahzadeh MH, Derakhshan A, Basiratnia M. The effect of renal transplantation on ventricular repolarization in children with chronic renal failure. *Int J Organ Transplant Med*. 2013;4(4):144-149.
2. Monfared A, Ghods AJ. Improvement of maximum corrected QT and corrected QT dispersion in electrocardiography after kidney transplantation. *Iran J Kidney Dis*. 2008;2(2):95-98.
3. Kim GB, Kwon BS, Kang HG, et al. Cardiac dysfunction after renal transplantation; incomplete resolution in pediatric population. *Transplantation*. 2009;87(11):1737-1743. doi:10.1097/TP.0b013e3181a63f2f
4. Scharer K, Schmidt KG, Soergel M. Cardiac function and structure in patients with chronic renal failure. *Pediatr Nephrol*. 1999;13(9):951-965. doi:10.1007/s004670050737
5. Kaidar M, Berant M, Krauze I, et al. Cardiovascular risk factors in children after kidney transplantation: from short-term to long-term follow-up. *Pediatr Transplant*. 2014;18(1):23-28. doi:10.1111/petr.12174
6. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Change in mortality risk over time in young kidney transplant recipients. *Am J Transplant*. 2011;11(11):2432-2442. doi:10.1111/j.1600-6143.2011.03691.x
7. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocardiol*. 2008;41(6):575-580. doi:10.1016/j.jelectrocard.2008.07.030
8. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol*. 2006;47(9):1828-1834. doi:10.1016/j.jacc.2005.12.049
9. Demirol M, Karadeniz C, Ozdemir R, et al. Prolonged Tp-e interval and Tp-e/QT ratio in children with mitral valve prolapse. *Pediatr Cardiol*. 2016;37(6):1169-1174. doi:10.1007/s00246-016-1414-7
10. Gupta P, Patel C, Patel H, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol*. 2008;41(6):567-574. doi:10.1016/j.jelectrocard.2008.07.016
11. Fujino M, Hata T, Kuriki M, et al. Inflammation aggravates heterogeneity of ventricular repolarization in children with Kawasaki disease. *Pediatr Cardiol*. 2014;35(7):1268-1272. doi:10.1007/s00246-014-0926-2
12. Yildiz A, Akkaya V, Tukek T, et al. Increased QT dispersion in hemodialysis patients improve after renal transplantation: a prospective-controlled study. *Transplantation*. 2001;72(9):1523-1526. doi:10.1097/00007890-200111150-00009
13. Koc M, Toprak A, Ozener IC, et al. QT dispersion in renal transplant recipients. *Nephron*. 2002;91(2):250-254. doi:10.1159/000058400
14. Arnol M, Starc V, Knap B, Potocnik N, Bren AF, Kandus A. Left ventricular mass is associated with ventricular repolarization heterogeneity one year after renal transplantation. *Am J Transplant*. 2008;8(2):446-451. doi:10.1111/j.1600-6143.2007.02083.x
15. Monfared A, Atrkar Roshan Z, Salari A, et al. QT intervals in patients receiving a renal transplant. *Exp Clin Transplant*. 2012;10(2):105-109. doi:10.6002/ect.2011.0117
16. Butani L, Berg G, Makker SP. QTc interval in children with chronic renal failure and with renal transplants. *Pediatr Nephrol*. 2002;17(1):6-9. doi:10.1007/s004670200001
17. Demir K, Konakci E, Ozkaya G, et al. New features for child metrics: further growth references and blood pressure calculations. *J Clin Res Pediatr Endocrinol*. 2020;12(2):125-129. doi:10.4274/jcrpe.galenos.2019.2019.0127
18. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol*. 2012;23(4):578-585. doi:10.1681/ASN.2011111115
19. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation*. 1977;55(4):613-618. doi:10.1161/01.cir.55.4.613
20. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr*. 2009;22(6):709-714. doi:10.1016/j.echo.2009.03.003
21. de Simone G, Daniels SR, Kimball TR, et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. *Hypertension*. 2005;45(1):64-68. doi:10.1161/01.HYP.0000150108.37527.57
22. Bozbas H, Atar I, Yildirir A, et al. Prevalence and predictors of arrhythmia in end stage renal disease patients on hemodialysis. *Ren Fail*. 2007;29(3):331-339. doi:10.1080/08860220701191237
23. Li W, Bai Y, Sun K, et al. Patients with metabolic syndrome have prolonged corrected QT interval (QTc). *Clin Cardiol*. 2009;32(12):E93-E99. doi:10.1002/clc.20416
24. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47(2):362-367. doi:10.1016/j.jacc.2005.08.067
25. Kuo CS, Atarashi H, Reddy CP, Surawicz B. Dispersion of ventricular repolarization and arrhythmia: study of two consecutive ventricular premature complexes. *Circulation*. 1985;72(2):370-376. doi:10.1161/01.cir.72.2.370
26. Yetkin E, Ileri M, Tandogan I, et al. Increased QT interval dispersion after hemodialysis: role of peridialytic electrolyte gradients. *Angiology*. 2000;51(6):499-504. doi:10.1177/000331970005100607
27. Morris ST, Galiatsou E, Stewart GA, Rodger RS, Jardine AG. QT dispersion before and after hemodialysis. *J Am Soc Nephrol*. 1999;10(1):160-163.
28. Hausberg M, Kosch M, Harmelink P, et al. Sympathetic nerve activity in end-stage renal disease. *Circulation*. 2002;106(15):1974-1979. doi:10.1161/01.cir.0000034043.16664.96
29. Alparslan C, Yavascan O, Dogan MS, et al. Pretransplant stable systolic cardiac functions play an important role in short-term systolic cardiac functions after kidney transplant in children. *Exp Clin Transplant*. 2017;15(1):34-39. doi:10.6002/ect.2015.0208
30. Mitsnefes MM, Schwartz SM, Daniels SR, Kimball TR, Khoury P, Strife CF. Changes in left ventricular mass index in children and adolescents after renal transplantation. *Pediatr Transplant*. 2001;5(4):279-284. doi:10.1034/j.1399-3046.2001.005004279.x
31. Hernandez D, Gonzalez A, Rufino M, et al. Time-dependent changes in cardiac growth after kidney transplantation: the impact of pre-dialysis ventricular mass. *Nephrol Dial Transplant*. 2007;22(9):2678-2685. doi:10.1093/ndt/gfm247
32. Ramoglu MG, Ucar T, Yilmaz S, et al. Hypertension and improved left ventricular mass index in children after renal transplantation. *Pediatr Transplant*. 2017;21(8):e13066. doi:10.1111/petr.13066
33. Himelman RB, Landzberg JS, Simonson JS, et al. Cardiac consequences of renal transplantation: changes in left ventricular morphology and function. *J Am Coll Cardiol*. 1988;12(4):915-923. doi:10.1016/0735-1097(88)90454-8

34. Johnson MC, So S, Marsh JW, Murphy AM. QT prolongation and Torsades de Pointes after administration of FK506. *Transplantation.* 1992;53(4):929-930. doi:10.1097/00007890-199204000-00040
35. Hodak SP, Moubarak JB, Rodriguez I, Gelfand MC, Alijani MR, Tracy CM. QT prolongation and near fatal cardiac arrhythmia after intravenous tacrolimus administration: a case report. *Transplantation.* 1998;66(4):535-537. doi:10.1097/00007890-199808270-00021
36. Erdogan I, Bilginer Y, Duzova A, Besbas N. Sinus tachycardia related to tacrolimus after kidney transplantation in children and young adults. *Turk J Pediatr.* 2015;57(6):587-591.