ORIGINAL ARTICLE

Tp-e interval and Tp-e/QT ratio in clinically stable pediatric heart transplant recipients

Klinik stabil çocuk kalp nakli alıcılarında Tp-e mesafesi ve Tp-e/QT oranı

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ABSTRACT

Objective: A study of the T wave peak-to-end (Tp-e) interval, the Tp-e/QT ratio, and the Tp-e/QTc ratio in pediatric heart transplant recipients (HTRs), a group which has a higher risk of sudden cardiac death than the normal population, has not previously been reported. The aim of this study was to assess alterations in ventricular repolarization using the Tp–e interval, Tp–e/QT ratio, and Tp–e/QTc ratio in clinically stable pediatric HTRs.

Methods: A total of 13 clinically stable HTRs, 13 patients who had undergone cardiac surgery (CS) under cardiopulmonary bypass, and 16 healthy controls under 18 years of age were retrospectively evaluated.

Results: No significant differences were observed between the HTR, CS, and control groups in terms of QTc, JTc interval, and T wave amplitude (p>0.05). The Tp-e interval (p=0.001), Tp-e/QT ratio (p<0.001), and Tp-e/QTc ratio (p=0.001) were significantly higher in the HTR group compared with the CS and normal control participants.

Conclusion: The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were elevated in stable HTRs compared with the normal and CS groups.

ÖZET

Amaç: Literatürde, ani kardiyak ölüm açısından normal popülasyondan daha riskli olan çocuk kalp nakli alıcılarında (KNA); T dalga tepe noktası ve sonu mesafesi (Tp-e), Tp-e/QT ve Tp-e/QTc oranlarını değerlendiren çalışma bulunmamaktadır. Bu çalışmanın amacı klinik olarak stabil çocuk KNA da Tp-e, Tp-e/QT ve Tp-e/QTc oranları kullanılarak ventriküler repolarizasyon farklılıklarının değerlendirilmesidir.

Yöntemler: Yaşları 18'den küçük; 13 klinik olarak stabil KNA, 13 kardiyopulmoner baypss altında kalp cerrahisi uygulanmış (KC) hasta ve 16 sağlıklı kontrol bu geriye dönük araştırma kapsamında değerlendirildi.

Bulgular: QTc, JTc mesafeleri ve T dalga amplitüdleri (p>0.05) açısından KNA, KC ve sağlam kontrol grupları arasında anlamlı fark saptanmadı. Tp-e interval (p=0.001), Tp-e/QT (p<0.001) ve Tp-e/QTc oranları (p=0.001) KNA grubunda, KC ve kontrol grubuna göre anlamlı olarak daha yüksekti.

Sonuç: Tp-e mesafesi, Tp-e/QT ve Tp-e/QTc oranları klinik olarak stabil çocuk KNA da, kalp cerrahisi uygulanmış çocuk hastalar ve sağlıklı çocuklara göre artmıştır.

There are studies in the literature about the rhythm of the denervated heart and electrocardiographic (ECG) changes in both adult and pediatric heart transplant recipients (HTRs). It has been well-documented that the resting heart rate is increased, heart rate variability is decreased, and ECG reveals intraventricular conduction delay, right bundle block, and atrial enlargement in this patient group.[1–3] However, there has not yet been a study of these unique and vulnerable patients who have a higher risk of sudden cardiac death (SCD) compared with the normal population to evaluate ventricular repolarization differences, which have been shown to be associated with the risk of SCD in various clinical conditions.[4,5]

Abbreviations:

ASD	*Atrial septal defect*
CS	*Cardiac surgery*
ECG	*Electrocardiography*
HTR	*Heart transplant recipients*
JTc	*Corrected JT interval*
QTc	*Corrected QT interval*
SCD	*Sudden cardiac death*
Tp-e	*T wave peak-to-end*
VSD	*Ventricular septal defect*

Received: August 26, 2018 *Accepted:* October 26, 2018

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The objective of this study was to evaluate the T wave peak-to-end (Tp-e) interval, Tp-e/QT ratio, and Tp-e/QTc ratio on an ECG to demonstrate ventricular repolarization differences in 3 pediatric groups: normal healthy children, patients who had undergone cardiac surgery (CS), and clinically stable pediatric HTRs.

METHODS

Study population

Clinically stable pediatric HTRs under 18 years of age and pediatric patients who underwent CS under cardiopulmonary bypass in our hospital between July 2013 and February 2017 were included in this study. Age- and gender-matched healthy children who were admitted before regular sports participation were included in this study as controls. ECG, echocardiography, and blood tests were performed 6 months after the procedures for the HTR and CS patients and were retrospectively evaluated using medical records. All of the patients were clinically stable during the evaluation. HTRs who had ≥grade 2R rejection findings according to the International Society for Heart and Lung Transplantation during routine cardiac biopsy or patients with cardiac failure were excluded from the study.[6] Histidine-tryptophan-ketoglutarate solution was used to preserve the graft. All of the heart transplants were performed by same surgical team using the bicaval technique, and all of the patients underwent the same standard immunosuppressive treatment protocol (basiliximab in induction, tacrolimus/cyclosporine A, mycophenolate mofetil, prednisone in maintenance). CS patients who had a residual shunt after an atrial septal defect (ASD) repair and those with more than a mild degree of residual regurgitation after a ventricular septal defect (VSD) repair were excluded from the study. Cardiac functions assessed with echocardiography were normal in all patients. None of the CS patients had hemodynamically significant valvular dysfunction or residual anatomic defects. Liver-renal function tests and blood counts were within normal ranges for all of the patients. A total of 13 CS patients (7 ASD repairs, 3 VSD repairs, and 3 aortic valve repairs), 13 HTRs, and 16 age-/gender-matched normal controls were evaluated. There were no findings suggesting cardiac disease during physical examination, ECG, or routine echocardiography in the control group. This study was approved by the ethics committee of Yuksek Ihtisas Heart-Education and Research Hospital.

Twelve-lead electrocardiography

A standard 12-lead ECG was performed with the patients in the supine position at 25 mm/second with an amplitude of 10 mm/mV. Patients with complete atrioventricular block and those with pre-excitation patterns were excluded. Lead V5 and lead D2 were selected for the analysis. The QT interval was defined as the interval between the beginning of the QRS and the end of the T wave. The interval between the peak and the end points of the T wave was considered the Tp-e interval. Duration of the Tp-e interval, QT interval, and QRS duration were measured manually on the leads with a caliper. These ECG measurements were performed by a pediatric cardiologist who was blinded to the patient data. The QT intervals were corrected using Bazett's (QTc) formula. The heart rate-corrected JT interval (JTc) was derived by subtracting the QRS duration from the heart rate-corrected QT interval (JTc = QTc – QRS duration).

Statistical analysis

Quantitative data were expressed as a median with interquartile range or mean value±SD. The distribution pattern of the data was evaluated via the Kolmogorov-Smirnov test. A chi-square test was used for comparisons between categorical data. Comparisons of groups were performed with a one-way analysis of variance and the Kruskal Wallis test, as appropriate. The statistical analyses were performed using SPSS Statistics for Windows, Version 17.0 software (SPSS Inc., Chicago, IL, USA). A p value of 0.05 was considered statistically significant.

RESULTS

General characteristics

In all, 13 HTR patients, 13 CS patients, and 16 healthy controls were evaluated within the scope of the study. The demographic characteristics of the groups are provided in Table 1. In the HTR group, 3 patients had undergone a heart transplant due to restrictive cardiomyopathy, 1 patient due to hypertrophic cardiomyopathy, and 9 patients due to dilated cardiomyopathy. None of the HTRs had ECG findings indicating a hereditary arrhythmia syndrome, such as long QT syndrome, catecholaminergic polymorphic ven-

tricular tachycardia, Brugada syndrome, or short QT syndrome. Some ECG changes that were attributed to their primary myocardial diseases (left bundle branch block, intraventricular conduction delay, atrial-ventricular enlargement findings, ventricular hypertrophy findings, and voltage suppression) had been observed in the HTRs before transplantation. Seven patients in the HTR group had undergone a left ventricular assist device procedure a mean of 42±33.3 days before transplantation, Pre-transplant pulmonary vascular resistance was 3.59±3 Wood Units. The mean graft ischemic time and cross-clamp time was 227.0±23.2 and 83.0±16.5 minutes, respectively. The mean duration of follow-up was 37.5±14.32 months for the HTR patients. One HTR patient died due to acute rejection 2 years after transplantation. There were no significant differences in age between the patients of the HTR, CS, and normal control groups (mean: 11.23 ±4.1, 13.34±2.79, 12.7±3.1 years, respectively; p=0.4).

The heart rate was significantly higher in the HTR group compared with that of the control and CS

Table 1. Main characteristics of the study groups

	Heart transplantation (n=13)	Cardiac surgery (n=13)	Control (n=16)	*p*
Age (years), mean±SD	11.23±4.1	13.34±2.79	12.7±3.1	0.4
Gender (male/female)	6/7	9/4	6/10	0.23
Weight (kg), mean±SD	39.1±20.7	49.7±13.1	49.06±16.6	0.2
Heart rate (bpm), mean±SD	100.7±16.1*	85.9±10.5	88.3±10.04	0.008
Fractional shortening (%), mean±SD	39.53±3.28	36.38±4.2	37.1±11.3	0.53
Hemoglobin (g/dL), mean±SD	11.9±1.99	12.6±1.76	13.1±1.05	0.1
Platelet (median, 25th and 75th, %, x10^{3}/µl)	293 (239.5–538.5)	243 (210–299)	286.5 (263–362.7)	0.07
BUN (mg/dL), mean±SD	34.46±9.2	28.3±7.26	27.18±4.8	0.03
Creatinine (mg/dL), mean±SD	0.71±0.21	0.61±0.18	0.60±0.14	0.27
AST (U/L), mean±SD	29.07±11.4	20.8±8.78	26.1±9.4	0.11
ALT (U/L), mean±SD	25±10.44	14.23±5.59	19.18±9.23	0.03
Na (mmol/L), mean±SD	140.07±2.66	138.76±2.38	139.87±2.98	0.4
K (mmol/L), mean±SD	4.1±0.69	4.15±0.38	4.22±0.4	0.8

BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Na: Sodium; K: Potassium; SD: Standard deviation; IQR: Interquartile range. Values are given as count (%), median with interquartile range, or mean±SD, as appropriate. P<0.05 is significant. *P<0.05 vs control and cardiac surgery group.

Table 2. Electrocardiographic parameters of groups

	Heart transplantation (n=13)	Cardiac surgery (n=13)	Control (n=16)	*p*
	Mean±SD	Mean±SD	Mean±SD	
QT (ms)	341.2±40.4	380±40.8	350±31.8	0.03
QTc (ms)	439.8±34.7	431.4±29.4	430.3±25.9	0.7
JTc (ms)	322.15±23.4	329.15±27.1	345.3±26.4	0.98
T wave amplitude (mv)	2.66±1.04	2.93±1.39	2.91±1.6	0.8
T peak-T end interval (ms)	111.69±20.2*	85.53±17.7	76.7±24.2	0.001
T peak-T end interval / QT	0.33±0.07*	0.23±0.04	0.22±0.07	<0.001
T peak-T end interval / QTc	0.25±0.05*	0.20±0.05	0.17±0.05	0.001

JTc: Corrected JT interval; QT: QT interval; QTc: Corrected QT interval; SD: Standard deviation. Values are given as mean±SD. P<0.05 is significant. *P<0.001 vs control and p<0.05 vs cardiac surgery group.

groups. No statistically significant differences were found in the other parameters.

ECG parameters

There were no significant differences between the HTR, CS, and control groups in terms of the QTc, JTc intervals, or T wave amplitude (p>0.05). The Tp-e interval (p=0.001), Tp-e/QT ratio (p<0.001), and Tp-e/QTc ratio (p=0.001) were significantly higher in the HTR group compared with the CS and control groups (Table 2). The differences in Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio between the groups are shown in Figure 1.

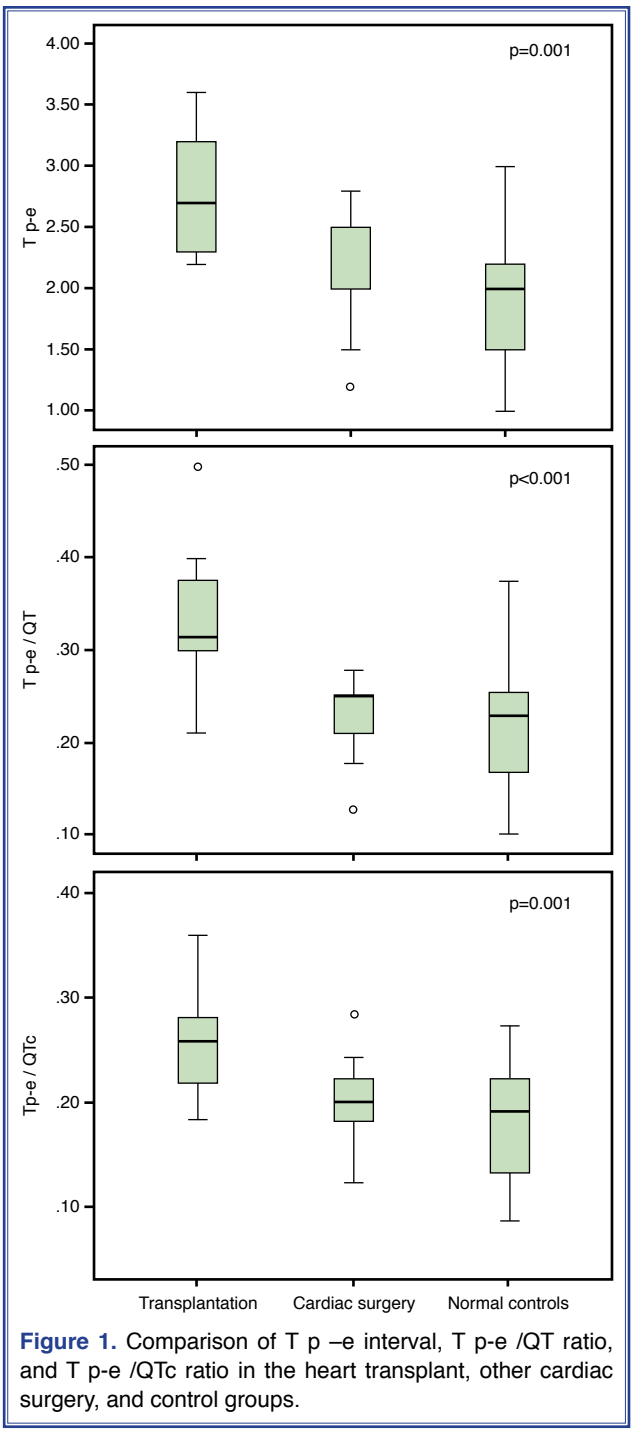

Figure 1. Comparison of T p –e interval, T p-e /QT ratio, and T p-e /QTc ratio in the heart transplant, other cardiac surgery, and control groups.

DISCUSSION

In this study, we demonstrated that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were elevated in clinically stable pediatric HTRs who had no evidence of rejection on biopsy in comparison with healthy children and pediatric patients who had undergone heart surgery. To the best of our knowledge, there is no previous study evaluating ventricular repolarization parameters in pediatric HTRs, or adult HTRs.

The ventricular myocardium is known to have a heterogeneous nature, consisting of 3 histologically similar, but electrically different, distinct cell groups.[7–9] There are differences in the action potential duration of the endocardial, epicardial, and subendocardial cells, which lead to transmural dispersion of repolarization. The Tp-e interval is defined as the interval between the peak and end points of a T wave, and reflects dispersion of repolarization.[10] The Tp-e interval and the Tp-e/QT ratio have been defined as the arrhythmogenic index in various cardiac pathologies, and they have been associated with a high risk of SCD.[11] Prolonged Tp-e intervals lead to an increase in arrhythmic risk. Increased dispersion of repolarization, predisposing to unidirectional block, namely reentry, is believed to be the cause of this effect. Hence, arrhythmogenic substrate occurs in these patients.[12–15] The incidence of SCD is increased in HTRs, accounting for 16% to 39% of deaths following transplant.[16–20] The cause of this elevated SCD incidence in HTRs is not clear. However, the incidence of atrial-ventricular arrhythmias, prolonged JTc intervals, an older donor, and increased heart rate have been associated with the risk of SCD in HTR.[21,22] In this study, we demonstrated that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were higher in the clinically stable pediatric HTRs compared with the healthy children and pediatric patients who underwent heart surgery. There may be several mechanisms that explain our results individually or in combination. Cardiac denervation occurring with a heart transplant is usually followed by incomplete cardiac reinnervation. This results in inadequate stimulation of the myocardial re-

ceptors, which may explain the different dispersion of repolarization seen in HTR.[23]

There are studies that have examined heart rate variability and reported that incomplete autonomic reinnervation is seen in adult and pediatric HTRs favoring sympathetic reinnervation.[24,25] Further follow-up studies are needed to better understand the effect of the sympathetic reinnervation seen in HTRs on Tp-e interval and Tp-e/QT ratio.

Cellular remodeling, which results from hypoxia and activation of renin–angiotensin/ transforming growth factor-beta systems seen in HTRs, may also be one reason for the difference in the Tp-e interval and Tp-e/QT ratio.[26] Other reasons may include immunosuppressive therapy and ischemia–reperfusion injury.[27]

ECG changes are expected in HTRs due to the rotation of the transplanted heart.[3,28] Therefore, the Tp-e interval and Tp-e/QT ratio might be different in HTRs compared with other groups as a result of this rotation.

The increased incidence of ventricular arrhythmias and SCD in HTRs may be due to the dispersion of repolarization, which was different from that of both the healthy pediatric group and the children who underwent CS. Prospective studies of HTRs will provide more accurate data. The limitations of this study include the single-center and retrospective design and a relatively small number of patients. In addition, the use of the same surgical technique and similar immunosuppressive therapy in each HTR in the study group is a limitation.

The increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in stable pediatric HTRs compared with healthy children and pediatric patients who have undergone CS may be an indicator of the dispersion of ventricular repolarization. This difference might also be associated with the greater of ventricular arrhythmias seen in HTRs. Prospective studies with larger patient populations are needed on this subject.

Ethics Committee Approval: The study was approved by the Ethics Committee of Yuksek İhtisas Heart-Education and Research Hospital (approval date: 24.01.2018, approval no.: 29620911-929).

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: S.K., F.A.P., S.K.; Design: S.K., S.K.; Supervision: F.A.P., U.K.; Materials: M.M.Z., D.E., D.E.S.; Data: M.M.Z., D.E., D.E.S.; Analysis: S.K., S.K.; Literature search: S.K., U.K.; Writing: S.K., F.A.P.; Critical revision: U.K., M.P.

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Keywords: Children; dispersion of ventricular repolarization; heart transplantation.

Anahtar sözcükler: Çocuklar; ventriküler repolarizasyon farklılığı; kalp nakli.