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A Valuable Tool in Predicting Poor Outcome due to Sepsis in Pediatric Intensive Care Unit: Tp-e/QT Ratio

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ABSTRACT

Objective: To assess the feasibility of 12-lead electrocardiographic (ECG) measures such as P wave dispersion (PWd), QT interval, QT dispersion (QTd), Tp-e interval, Tp-e/QT and Tp-e/QTc ratio in predicting poor outcome in patients diagnosed with sepsis in pediatric intensive care unit (PICU).

Methods: Ninety-three patients diagnosed with sepsis, severe sepsis or septic shock and 103 age- and sex-matched healthy children were enrolled into the study. PWd, QT interval, QTd, Tp-e interval and Tp-e/QT, Tp-e/QTc ratios were obtained from a 12-lead electrocardiogram.

Results: PWd, QTd, Tp-e interval and Tp-e/QT, Tp-e/QTc ratios were significantly higher in septic patients compared with the controls. During the study period, 41 patients had died. In multivariate logistic regression analyses, only Tp-e/QT ratio was found to be an independent predictor of mortality.

Conclusion: The ECG measurements can predict the poor outcome in patients with sepsis. The Tp-e/QT ratio may be a valuable tool in predicting mortality for patients with sepsis in the PICU.

KEYWORDS: sepsis, pediatric intensive care unit, Tp-e/QT ratio, mortality.

INTRODUCTION

Sepsis is the host's response to an infection that can be detrimental. Severe sepsis and septic shock are urgent health problems with increasing incidences, annually affecting millions of people around the world [1, 2]. Even in developed countries, sepsis is responsible for 10% of mortality for children aged <4 years and for 20% of cases requiring follow-up in intensive care [3]. As a result of elevated cytokine levels in the septic process, activated cascades lead to endotelial damage, fever, increased vascular permeability, disseminated intravascular coagulation and myocardial dysfunction [4, 5]. In this hyper-inflammatory state, the combination of depressed myocardial function and resuscitation with excessive fluid volume results in an increase in the left-ventricular end-diastolic pressure, thus creating tension in the left atrium [6, 7]. These pathological changes in the atrial and ventricular myocardium may lead to rhythm disturbances in patients with sepsis. Therefore, cases with

atrial and ventricular arrhythmias may be more prone to cardiovascular instability and inadequacy of medical supportive therapy, especially in ICU. The predictive roles of P wave dispersion (PWd), corrected QT interval (QTc), QTc dispersion and QT dispersion (QTd) on atrial and ventricular arrhythmias and all-cause mortality have been demonstrated. Increased P-wave dispersion reflects the tendency of atrial myocardium to rhythm disturbances such as atrial flutter and fibrillation. QT, QTd and QTc are indices of spatial dispersion of ventricular recovery time. Previously reported studies showed that patients with increased QT and QTd were more prone to ventricular arrhythmias and even sudden cardiac death (SCD) [7–13]. In recent years, Tp-e interval, Tp-e/QT ratio has emerged as novel noninvasive electrocardiographic (ECG) marker of dispersion of ventricular repolarization. Researchers have stated that prolonged Tp-e interval and increased Tp-e/QT, Tp-e/QTc ratios are related to tendency of ventricular arrhythmias and SCD [14].

This study aims to assess the impact and feasibility of 12-lead ECG measures, such as PWd, QT interval, QTd, QTcd, Tp-e interval, Tp-e/QT and Tp-e/QTc ratio, in predicting mortality in patients with sepsis, severe sepsis or septic shock, but without echocardiographically proven heart failure, in pediatric intensive care unit (PICU). To our knowledge, no similar report has previously appeared in the literature.

METHODS

Study population

From 2010 to 2015, a total of 102 patients were diagnosed with sepsis, severe sepsis or septic shock in the PICU in Izmir Dr. Behcet Uz Children's Hospital and were enrolled into this retrospective observational study. Patients' demographic features, capillary refill time (CRT), C-reactive protein (CRP), procalcitonin and lactate levels at the time of diagnosis were obtained from the patient data system. Diagnoses of sepsis, severe sepsis and septic shock were made according to the guidelines entitled, 'Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012' [15]. After the patients were admitted to the PICU, a modified Glasgow Coma Score (GCS) [16] was calculated within the first hour, and the Pediatric Risk of Mortality (PRISM III) Score was calculated within the first 24 h [17]. All of the participants underwent echocardiographic examination performed by a pediatric cardiologist. A Vivid 3 Pro Ultrasound System (GE Medical Systems, NE, USA) with 3 and 5 MHz transducers were used for two-dimensional and color flow Doppler echocardiography.

Patients were excluded if they used any medication that disturbs QT duration, or if they had electrolyte imbalances causing QT elongation (hypopotasemia, hypocalcemia, hypomagnesemia). Also excluded were patients with hypothermia, congenital heart disease or a history of dysrhythmia. Patients with evident heart failure on echocardiographic examination were excluded as well. The control group consisted of 103 healthy children of identical age and gender who were referred to our outpatient clinic for evaluation of murmur. The study was approved by the ethical committee of Izmir Dr. Behcet Uz Children's Hospital.

Electrocardiography

The standard 12-lead ECG (Cardiofax GEM, Model 9022 K; Nihon Kohden Tokyo, Japan) was recorded at a speed of 25 mm/s and an amplitude of 1 mV/cm while the patients were lying in a supine position right after the diagnoses were made. P-wave dispersion (PWd), QT interval, QTd, QTcd, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were calculated. To increase accuracy of the measurements, ECG recordings were scanned and transferred to a personal computer. After x400 zooming in Adobe Photoshop software, assessments were made directly from the ECG tracing by two pediatric cardiologists who were blinded to the data. No significant discrepancy was present between investigators. The interobserver variance for each measurement ranged between 5% and 12%.

P-wave dispersion: We defined the onset of the P-wave as the junction between the isoelectric line and the beginning of the P-wave deflection, and the offset of the P-wave as the junction between the end of the P-wave deflection and the isoelectric line. We calculated the dispersion of the P-wave as the

difference between the maximum and minimum P-wave durations (P-wave dispersion: maximum P-wave duration–minimum P-wave duration) [18]. P waves from all 12 leads were measured and used for calculation.

QT dispersion: We measured the QT interval from the beginning of the QRS complex to the end of the T-wave, but did not measure the QT interval if the T-wave was absent. If T-waves had two peaks and the second was <50% of the first one, then the point where the first peak reached the isoelectric line was assumed to be the end of the T-wave. For every patient, we calculated the corrected QT (QTc) interval regarding the previous cardiac cycle length according to the Bazzet formula [19]. An ECG recording was considered as analyzable when the QT interval could be measured in >8 leads. QT dispersion was calculated in available leads at least in 8 of 12 leads. These leads usually included lead I, II and V5. We calculated QT dispersion as the difference between the maximum and minimum QT interval.

Tp-e interval: Tp-e was measured from Tp (highest point of the T-wave, T-wave with maximum amplitude) to Te. We defined Te as the intersection point of the tangent to the down slope of the T-wave and isoelectric line. If a lead contained inverted T-waves, the measurement was taken from the lowest point of the inverted T-wave to Te. The U-wave was not taken into consideration [20].

Statistical analysis

The SPSS 15.0 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis. First, we compared all of the numeric and categorical data with descriptive statistics and evaluated the distribution pattern of numerical data using graphic methods (histogram or probability graphics) or analytic methods like the Kolmogorov–Smirnov test. Values are expressed as mean ± SD, median (interquartile range) or number (percentage) where appropriate. To compare normally distributed numerical data, we used Student's *t*-test for independent groups; if there were more than two groups, we used one-way variance analyses. To compare two groups with abnormally distributed numerical data, we used the Mann–Whitney U-test, and if there were more than two groups with abnormally distributed data, we used the Kruskal–Wallis test. Chi-square analysis was used for comparison of categorical variables, and associations between parameters were assessed using Spearman's correlation test. A p value <0.05 was considered statistically significant. The logistic regression test was used for determining the cause and effect relationship with the explanatory variables in binary (diotom) and multiple (multinominal) categories of the categorical response variable. Hosmer–Lemeshow was used to assess goodness of fit for the logistic regression model.

RESULTS

Ninety-three sick and 103 healthy children were enrolled in our study. Table 1 presents the demographic findings, CRP, procalcitonin, lactate levels, CRT, GCS and PRISM III scores of the study's participants. When we compared ECG findings of the study group with the control group, we found that PWd and QTd were higher in the study group ($p < 0.001$). Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were also significantly higher in septic patients compared with the controls ($p < 0.001$, $p < 0.001$ and $p = 0.003$, respectively; Table 2).

We found that, of the 93 patients, 35 were with sepsis (37.6%), 39 with severe sepsis (41.9%) and 19 with septic shock (20.4%). These groups were compared in terms of PWd, QTd, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios. We could not find any difference between the groups. Additionally, we did not find any difference between severe sepsis and septic shock patients in terms of these parameters, as well (Table 3).

When we investigated the relationship between the ECG findings and the inflammatory markers, we found a significant and positive correlation between the CRP and both the Tp-e interval and Tp-e/QTc ratio. However, there was no correlation between any ECG findings and procalcitonin (Table 4). When we compared the sufficiency of the peripheral circulation and ECG findings, the ECG findings did not correlate with lactate levels. However, we found that there was a positive correlation between prolonged CRT and both Tp-e interval and Tp-e/QTc ratio (Table 4).

Table 1. Age and clinical and laboratory features

Variables	Patients ($n = 93$) (Median, IQR, min-max)	Healthy controls ($n = 103$) (Median, IQR, min-max)	p
Age (month)	33, 30, 1–108	35, 31, 1–108	0.84
PRISM	12, 14, 4–51		
GCS	10, 5, 3–12		
CRT (s)	3, 4, 1–7		
Lactate (mg/dl)	2.2, 3, 0.8–42.4		
CRP (mg/dl)	8, 11.8, 0.01–39.7		
Procalcitonin (ng/ml)	6.6, 25.8, 0.05–200		

Notes. CRP = C-reactive protein; CRT = capillary refill time; GCS = Glasgow coma scale; PRISM = Pediatric Risk of Mortality score.

Table 2. A comparison of electrocardiographic findings of the patients and healthy controls

Characteristics	Patients ($n = 93$)	Healthy controls ($n = 103$)	p
PW dispersion (ms)[a]	40, 22, 10–100	20, 30, 5–80	<0.001
QT dispersion (ms)[a]	40, 24, 10–150	29.5, 20, 8–60	<0.001
Tp-e interval (ms)[b]	76.6 ± 23.2	60.3 ± 13.2	<0.001
Tp-e /QT[b]	0.27 ± 0.05	0.17 ± 0.04	<0.001
Tp-e/QT_c[b]	0.2 ± 0.05	0.16 ± 0.03	0.003

[a]Data are expressed as median, interquartile range, min-max.
[b]Data are expressed as mean ± SD.

Table 3. Comparison of ECG characteristics of patients according to the diagnosis

Characteristics	Sepsis (A) ($n = 35$, 37.6%)	Severe sepsis (B) ($n = 39$, 41.9%)	Septic shock (C) ($n = 19$, 20.4%)	P (A-B-C)	P (B-C)
PW dispersion (ms)[a]	40, 20 (10–60)	40, 20 (10–70)	40, 20 (20–100)	0.94	0.76
QT dispersion (ms)[a]	40, 20 (20–150)	40, 30 (20–80)	40, 60 (20–80)	0.41	0.20
Tp-e interval (ms)[a]	80, 30 (40–100)	80, 30 (40–120)	70, 30 (30–200)	0.65	0.39
Tp-e/QT[b]	0.24 ± 0.05	0.25 ± 0.05	0.24 ± 0.09	0.43	0.37
Tp-e/QT_c[b]	0.17 ± 0.05	0.18 ± 0.04	0.19 ± 0.08	0.97	0.83

[a]Data are expressed as median, interquartile range, min-max.
[b]Data are expressed as mean ± SD.

Patients with low GCS had increased Tp-e/QT and Tp-e/QTc ratios. We found a significant and positive correlation between the PRISM III mortality score and Tp-e interval; meanwhile, there was a significant correlation between the PRISM III mortality score and the Tp-e/QT and Tp-e/QTc ratios. During the follow-up period, 60 (58.8%) patients were discharged, while 42 (41.2%) had died. We did not encounter any significant arrhythmia in any of our patients. When we compared the survivors' and the deceased children's ECG findings at the time they were diagnosed, we found that the deceased children had statistically significant higher Tp-e/QT and Tp-e/QTc ratios than the survivors (Table 5). Deaths according to the subgroups are shown in Table 6. Among all variables determined in the study group, only Tp-e/QT ratio could be included in the multivariable model ($p = 0.016$, OR: 2.12; 95% CI: 1.31–3.98).

Table 4. Correlation between ECG parameters and clinical/laboratory findings

ECG parameters	CRP		Procalcitonin		Lactate		CRT		GCS		PRISM	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
PW dispersion	0.04	0.86	0.003	0.98	0.062	0.69	0.031	0.92	−0.142	0.38	0.0043	0.89
QT dispersion	0.07	0.42	0.053	0.72	0.23	0.34	0.09	0.33	0.023	0.93	0.09	0.34
Tp-e interval	0.280	0.012	0.18	0.22	0.168	0.22	0.234	0.03	0.174	0.24	0.237	0.022
Tp-e/QT	0.12	0.21	0.043	0.64	0.14	0.32	0.272	0.006	−0.26	0.012	0.312	0.002
Tp-e/QT_c	0.253	0.01	0.12	0.24	0.11	0.32	0.162	0.07	−0.214	0.03	0.36	0.002

Notes. CRP = C-reactive protein; CRT = capillary refill time; GCS = Glasgow coma scale; PRISM = pediatric risk of mortality score.

Table 5. A comparison ECG findings of survivors and nonsurvivors

Characteristics	Survivors ($n = 52$)	Nonsurvivors ($n = 41$)	*p*
PW dispersion (ms)[a]	40, 20, 10–100	35, 20, 10–70	0.41
QT dispersion (ms)[a]	40, 20, 10–150	40, 30, 20–80	0.58
Tp-e interval (ms)[b]	75 ± 26.3	72.7 ± 26	0.40
Tp-e/QT[b]	0.22 ± 0.05	0.27 ± 0.04	0.01
Tp-e/QT_c[b]	0.14 ± 0.06	0.19 ± 0.06	0.011

[a]Data are expressed as median, interquartile range, min-max.
[b]Data are expressed as mean ± SD.

Table 6. Deaths according to the groups

	Sepsis	Severe sepsis	Septic shock
Nonsurvivor (*n*/%)	9/25.7	20/51.3	12/63.2
Survivor (*n*)	26	19	7
Total (*n*)	35	39	19

DISCUSSION

The Tp-e interval and Tp-e/QT and Tp-e/QTc ratios are markers for total variability in the heart repolarization [21]. Previously reported studies have showed that Tp-e interval, Te/QT and Tp-e/QTc ratios are higher in long QT syndrome, Brugada syndrome and myocardial infarction [22–24]. Unlike Tp-e interval, Tp-e/QT ratio is not influenced by heart rate and body weight and thus has been considered as a superior marker of ventricular repolarization [11, 25]. There are limited data on the reference range of Tp-e interval and Tp-e/QT ratio in healthy children. Benatar and Carbonez [26] found that mean Tp-e interval between the age 5 and 10 years was 71 ± 8.1 ms and beyond 10 years of age mean Tp-e interval was 76 ± 8.4 ms in lead II. These authors stated that mean Tp-e/QT ratio was 0.21 ± 0.02 for both age groups, 5–10 years and >10 years Accumulating data has demonstrated that prolonged Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are associated with ventricular arrhythmias and SCD [14, 27]. In this study, we demonstrated that Tp-e interval, Tp-e/QT, Tp-e/QTc ratios were significantly prolonged in septic patients compared with the controls. Also we showed that Tp-e/QT ratio was an independent predictor of mortality in patients with sepsis. Elevated cytokine levels, hyper-inflammatory state, abnormal catecholamine regulation and inotropic support may lead to ventricular repolarization abnormality. While our study design did not permit evaluation of ventricular arrhythmic events and among patients with sepsis and septic shock, and pathophysiological linking Tp-e interval and Tp-e/QT ratio to ventricular arrhythmias, we did not encounter any significant life-threatening arrhythmic event in any of our patients with prolonged Tp-e/QT ratio. To our knowledge,

our study is the first to demonstrate the correlation between the Tp-e/QT ratio and mortality in patients diagnosed with sepsis. We could not find any difference between the groups sepsis, severe sepsis and septic shock in terms of Tp-e interval, Tp-e/QT and Tp-e/QTc ratios. Our results suggested that Tp-e interval and Tp-e/QT ratio are may be useful markers of mortality risk for certain specific conditions.

A new ECG marker, PWd, has been studied in patients with acute rheumatic fever, aortic stenosis, hypertension, renal failure and paroxysmal AF. Patients with increased PWd were found to be at higher risk for atrial fibrillation [12, 28–30]. Some reports stated that PWd over the 60 ms have strong correlation with AF [29]. In our study, PWd was significantly higher in the patient group compared with the control group; however, we did not detect any supraventricular arrhythmia during their treatment in the PICU. On the other hand, there was no difference in the PWd of the patients who had died and those who had survived.

The CRP is one of the earliest sepsis biomarkers, which is produced by the hepatocytes in the inflammatory state. Many roles have been postulated for CRP, including acting as a marker of subclinical inflammation that damages myocardium and causes myocardial fibrosis. Myocardial fibrosis is a potential substrate for a re-entrant ventricular tachyarrhythmia, a significant cause of SCD [31]. When we compared the ECG measurements and CRP, we found that CRP had a positive correlation with Tp-e interval and Tp-e/QTc ratio.

The diagnostic superiority of procalcitonin over CRP has been controversial. However, research has shown procalcitonin to reach peak concentrations in the setting of inflammation before CRP. Many studies have emphasized that procalcitonin is superior to CRP as an indicator of sepsis and septic shock, especially at the time of admission to the hospital. It also correlates with the severity of the disease [32, 33]. Surprisingly, in our study, we could not find any statistical correlation between the ECG findings and procalcitonin.

The PRISM III scoring system has been used to estimate the prognosis of the patients admitted to the PICU. It uses 17 clinical or laboratory variables to predict the probability of death for the patient. Many studies have shown that PRISM III is one of the best scoring systems for estimating prognosis [34, 35]. In our study, we found that high PRISM III scores had a significant positive correlation with Tp-e interval, Tp-e/QTc and Tp-e/QT ratios, whereas a low GCS only correlated with Tp-e/QTc and Tp-e/QT ratios.

CRT is a simple method that has been implemented for assessing the microvascular perfusion in patients with septic shock. Recently, it has also been incorporated into pediatric advanced life support guidelines. Children with prolonged CRT were reported to be at high risk for a serious disease [36]. An adult study evaluating 64 patients with septic shock revealed that after the initial resuscitation of septic shock, CRT was a strong predictor of 14 day mortality [37]. We found a positive correlation between CRT and Tp-e interval and Tp-e/QT ratio in our study group.

Lactate levels increase owing to anaerobic metabolism or lack of lactate utilization in patients with sepsis and septic shock. Many studies have defined a positive correlation between lactate concentrations and mortality [38, 39]. Marty *et al.* [40] evaluated 96 patients with severe sepsis and septic shock, reporting that the lactate concentration and lactate clearance in the first 24 h of sepsis and septic shock were the best parameters correlated with 28 day mortality. Unlike CRT, in our study, we did not found any relationship between lactate concentration and ECG findings.

CONCLUSION

However, we could not find any difference between the groups sepsis, severe sepsis and septic shock in terms of Tp-e interval, Tp-e/QT and Tp-e/QTc ratios. These markers still might be associated with disease severity in patients with sepsis in the PICU because they were significantly associated with high CRP, CRT, PRISM score and low GCS. The Tp-e/QT ratio may be a particularly valuable tool in predicting mortality for patients with sepsis in the PICU. However, prospective randomized trials with larger series are needed for this consideration to become practically feasible.

Limitations

A number of patients needed inotropes to maintain normal blood pressure levels. Given the inotropes affect QT interval and heart rate and thus QTc calculation, our results might be affected by inotropic medication.

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