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Evaluation of T-wave alternans in pediatric patients with chronic renal failure

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ABSTRACT

Introduction: Microvolt T-wave alternans (TWA) is known to be useful in prediction of ischemia and sudden death in high-risk populations and there are no studies in children with chronic renal failure (CRF). Cardiac problems seem to be responsible for an important part of death in children and young adults with CRF. The aim of this study is to evaluate Holter microvolts TWA measurements in children with CRF comparing to the control group.
Methods: This prospective study included 40 patients with CRF and 48 healthy controls. The history, echocardiography and microvolt TWA values based on 24-hour ECG recordings of the patients were evaluated. Analysis of microvolt TWA was considered on the basis of three leads (V5, V1 and AVF).
Results: Compared with the controls, the mean systolic and diastolic blood pressure values and average heart rates were significantly higher in the children with CRF ($p = 0.001$ and $p = 0.026$, respectively). Also, the values of left ventricular internal dimensions at end diastole and end-diastolic volume were significantly higher in CRF group ($p = 0.01$ and $p = 0.049$, respectively) and couplet ventricular extrasystole was detected in 2 patients with CRF. Consequently, all TWA values in three leads were increased in CRF group than the control group but the only increase in V5 lead was statistically significant ($p = 0.028$).
Conclusions: This study has demonstrated that microvolt TWA values increased in pediatric patients with CRF. TWA might be used for early risk assessment in pediatric patients with CRF in the future.

Introduction

Cardiac problems are responsible for an important part of death in children and young adults with chronic renal failure (CRF) [1,2]. Several clinical parameters and non-invasive tests have been developed to determine the risk of sudden cardiac death. Previous studies have been demonstrated that myocardial ischemia can increase T-wave alternans (TWA) magnitude, as was evidenced in animals during coronary artery occlusion and in humans during angioplasty [3,4]. Thus, microvolt TWA test, based on the measurement of changes resulting in the level microvolt T-wave from beat to beat on the electrocardiography (ECG), is non-invasive diagnostic method used in risk stratification of patients at sudden cardiac death [5,6].

T-wave alternans is an electrophysiological event manifested by ST-T wave morphology changes in successive pulses on ECG. TWA analysis can also be used in determining cardiovascular and sudden cardiac death risk in patients with reduced left ventricular ejection fraction. It has been reported that microvolt TWA test is used to identify the high arrhythmic mortality risk of the patients with cardiomyopathy or myocardial infarction (MI) history with a very high negative predictive value [7].

Structural parameters such as decreased left ventricular ejection fraction and the determination of myocardial scar, autonomic tone measurements such as heart rate variability, heart rate turbulence and baroreceptor sensitivity, and signal averaged ECG method have been used in order to identify the patients at sudden cardiac death risk. Recently, microvolt TWA has also been used in the evaluation of patients with this risk and there are some ongoing studies, as well [6]. Microvolt TWA analysis used in determining the risk of sudden cardiac death can be made in two ways: The first technique has been performed during the exercise whereas the second one has been performed with Holter recordings more recently [5]. This process is important for the implementation of TWA especially in cases with low exercise capacity or contraindicated efforts and children. On the basis of the fact, Holter recordings have been preferred for the study.

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In adult patients, it has been demonstrated that features of uremic cardiomyopathy are associated with an abnormal microvolt TWA results [8]. Moreover, due to the uremia effects on the heart, life-threatening ventricular tachyarrhythmias may also develop in pediatric patients with CRF. Most of the TWA studies have been performed in adults but there are no studies in children with CRF. Thus, the aim of this study is to evaluate Holter microvolts TWA measurements in children with CRF comparing with the control group.

Materials and methods

This prospective study included 40 CRF patients who had different dialysis program in the Department of Pediatric Nephrology, Mersin University School of Medicine, between January 2006 and December 2013 and 48 healthy children, similar to patient group in terms of age and gender, admitted to the Department of Pediatric Cardiology with innocent murmurs who do not have any cardiac pathology. Patients enrolled into the study after a complete physical examination including the blood pressure measurement, and echocardiographic examination (ECHO) and TWA analysis were performed. Healthy children, selected as a control group enrolled into the study after getting confirmed with no cardiac pathologies by ECHO. In Holter recordings, the isolated ventricular and supraventricular ectopics which were <10% regarded as insignificant arrhythmias [9]. One patient who had arrhythmia compatible with Wolff-Parkinson-White from the control group excluded the study and the group consisted of 47 children. Mersin University Ethics Committee approved this study (2012/66) and written informed consent was obtained from the parents of the patients. All CRF pediatric patients in the dialysis program at our institution across the 8 years between January 2006 and December 2013 asked to participate with the exclusion criteria. The patients with congenital heart diseases that might affect the heart (connective tissue diseases, muscle diseases, etc.), cardiotoxic drug history and endocrinological abnormalities (such as hyperthyroidism and diabetes mellitus) as well as the ones using anti-arrhythmic drug (beta adrenergic blockers, amiodarone, sotalol, etc.) were excluded from the study. Besides, the CRF patients who hospitalized due to infection were also excluded.

Blood pressure measurement

The measurement of systolic and diastolic blood pressures of the patients and the control group were performed through age-appropriate cuff after the 5-minute rest period with particular attention at heart level. When considering age and gender characteristics, the values above 95 percentile were accepted as hypertension.

ECHO evaluation

ECHO examinations of the patients were performed by the same pediatric cardiologist (Vivid S5 ECO device G VINGMED Horten, Norway). 3S sector probe was used and ECHO was performed at supine position. According to the recommendations of the American Society of Echocardiography, the ventricular function and wall thickness were recorded by M-mode analysis using the apical 4-chamber and parasternal long-axis images in line. Left ventricular volume measurements were performed using the single plane Simpson's method. The rates of early and late diastolic flow velocity were measured by tissue Doppler method.

Holter ECG and microvolt TWA measurement

A 24-hour Holter electrocardiography (ECG) monitoring was done by use of a digital recording device (Seer MC) produced by GE Medical Systems, Nagoya, Japan. Measurements were taken from 3 derivations including V1, V5 and AVF. The sample rate was selected as 128 Hz. Analysis of Microvolt TDA was performed as the maximum TWA analysis via software coded version 7.2 produced by Mars PC systems. The method used for analysis was time-domaining MMA (Modified moving average) method, which is the generation and display of high-resolution QRS-aligned templates of superimposed ECG complexes [6]. TWA was analyzed from routine 24-hour Holter ECG recording based on V1, V5 and AVF leads. Modified V5 was recorded at lead 1, modified V1 at lead 2 and AVF recorded at lead 3. Maximal TWA voltages were recorded automatically in each of the three leads when heart rate was lower than 160 per minute.

Statistical analysis

Controls of normality for the continuous measurements were tested by the “Shapiro Wilk” test. “Student t test” and “Mann-Whitney U” tests were used for between-group differences for continuous measurement. Descriptive values were given as means ± standard deviation (SD) for normal distribution. “Spearman correlation coefficient” was used for the relationship between continuous measurements. “Chi-square” and “likelihood ratio chi-square” tests were used for differences between categorical variables. Descriptive statistics were given as the number and percentage values. Statistical significance was accepted as $p < 0.05$.

Results

This study included 40 patients with CRF and 47 healthy children aged between 7 and 18 years. The mean age of children was 13.8 ± 3.6 years for patients with CRF and 12.5 ± 3 years for control group (Table 1). No statistically significant differences were found between patients and control groups regarding the gender and age ($p = 0.521$ and $p = 0.07$, respectively). Patients with CRF were grouped according to the dialysis need and type. Thus, 12 patients (30%) had hemodialysis, 8 patients (20%) had peritoneal dialysis; however, 20 patients (50%) were not on dialysis. Of those, 10 (50%) had stage 1 CRF, 8 (40%) had stage 2 CRF and 2 (10%) had stage 3 CRF. Compared with the controls, the mean systolic and diastolic blood pressure values and average heart rates were significantly higher in the children with CRF (Table 1).

In our study, we have found out arrhythmia in 14 (35%) of the patients most of whom were supraventricular (25%). Only 4 patients (10%) had ventricular arrhythmia two of whom had “couplet VES” and beta adrenergic blocker was started. During the Holter recordings, these patients were not using beta adrenergic blockers. Except these patients, all of the arrhythmias were insignificant thus no treatment required. ECHO findings of CRF and control groups have been demonstrated in Table 2. Although left ventricular internal dimension at end-diastole (LVEDD), left ventricular internal dimension at end-systole (LVESD), end-diastolic volume (EDV) and end-systolic volume (ESV) values were higher in CRF group, only the values of LVESD and EDV were statistically significant. In terms of diastolic function, only mitral-E and mitral-A values were significantly increased and E/A value was decreased in CRF group. Table 3 showed ECG information for CRF patients and control subjects.

Comparison of the maximum T-wave alternans values of CRF and control groups was shown in Fig. 1. When TWA values of the patients were compared, maximum TWA values obtained from V5 lead were

Table 1
Characteristics of the patient and control groups.

	CRF n = 40	Control n = 47	p
Age (year, mean ± SD)	13.8 ± 3.6	12.5 ± 3	0.07
Gender (male/female)	22/18	22/25	0.521
SBP (mmHg, mean ± SD)	136 ± 15.7	105 ± 10.5	**0.001**
DBP (mmHg, mean ± SD)	85 ± 11.8	64 ± 9.3	**0.001**
HR (per minute, mean ± SD)	92 ± 16	86 ± 8	**0.026**

CRF; Chronic renal failure, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, HR; Heart rate.
Bold values indicate significance at $p < 0.05$.

Table 2
Comparison of Echocardiographic findings.

	CRF n = 40	Control n = 47	p
LVEDD (cm)	4.19 ± 0.76	3.98 ± 0.61	0.146
LVESD (cm)	2.98 ± 0.67	2.64 ± 0.53	**0.01**
IVSd (cm)	0.79 ± 20	0.82 ± 0.19	0.495
LVPWd (cm)	0.86 ± 18	0.80 ± 17	0.166
EF (%)	64.8 ± 6.08	63.5 ± 9.5	0.443
EDV (mL)	81.4 ± 32	68.9 ± 26.2	**0.049**
ESV (mL)	31.9 ± 13.8	26.9 ± 14.4	0.106
Mitral.E (m/min)	0.93 ± 0.17	0.83 ± 0.18	**0.016**
Mitral.A (m/min)	0.65 ± 0.16	0.52 ± 0.09	**0.0001**
E/A	1.48 ± 0.35	1.65 ± 0.30	**0.029**

LVEDD, left ventricular internal dimension at end-diastole; LVESD, left ventricular internal dimension at end-systole; IVSd, interventricular septum thickness at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume.
Bold values indicate significance at $p < 0.05$.

significantly higher in patients with CRF ($p = 0.028$). Although CRF patients had slightly higher TWA values in the V1 and AVF leads recordings, the differences were not statistically significant. Consequently, all TWA values in three leads were increased in CRF group comparing with the controls where only statistically significant increase was in lead V5 (Figs. 1, 2).

When the relationships between ECHO findings and TWA measurements were examined for all children, the values of LVEDD, LVESD, EDV and ESV were positively correlated with lead V1 TWA values ($r = 0.412$, $r = 0.353$, $r = 0.431$, and $r = 0.352$; $p = 0.0001$, $p = 0.001$, $p = 0.0001$ and $p = 0.001$, respectively). Besides, TWA values of lead V5 and lead AVF were only positively correlated with LVESD values ($p = 0.023$ and, $p = 0.025$ respectively).

On the other hand, comparing the relationships between ECHO findings and TWA measurements of CRF patients, the values of LVEDD, LVESD and EDV were positively correlated with both lead V1 ($r = 0.456$, $r = 0.336$, and $r = 0.451$; $p = 0.003$, $p = 0.034$, and $p = 0.003$, respectively) and lead V5 TWA values ($r = 0.324$, $r = 0.395$, and $r = 0.344$; $p = 0.041$, $p = 0.012$, and $p = 0.030$, respectively). However, ESV values were positively correlated with only lead V1 TWA values ($r = 0.343$, $p = 0.030$) where ECHO parameters had no correlation with the values of leads AVF TWA. These findings demonstrated fluid overload and high volume in heart especially increased in the values of leads V1 and V5.

Discussion

The cardiovascular diseases in children and young adults with CRF have been increasing due to successful implementation of renal replacement therapy with long survival rates. Cardiac problems seem to be responsible for a significant proportion of deaths in children and young adults with CRF [1,2] since cardiovascular damages start in the predialysis period and go on during the dialysis process. The cause of death in 51% of children treated with dialysis and 37% of children with kidney transplant are cardiovascular diseases. Despite of the fact, causes of cardiac mortality have not been clearly established [5,10]. Therefore, cardiovascular system should be evaluated with non-invasive and rapid diagnostic screening methods in children with CRF [11]. Consequently, microvolt TWA test based on the measurement of changes resulting in the level microvolt T-wave on the ECG is a non-invasive diagnostic method used in risk stratification of the patients [6]. In this study, Holter microvolts TWA measurements in children with CRF were compared with the control group.

Although, hypertension is a risk factor for ischemic heart disease, heart failure and left ventricular hypertrophy in adults [12], the effect of it in children with CRF is controversial [13]. A study in children with pre-dialysis CRF reported that there was no significant relationship between blood pressure and left ventricular mass index (LVMI) [14]; whereas, another prospective study found out that increased systolic blood pressure especially at night was an alone risk factor for the increase of LVMI [13]. In an observational cohort study, 586 children with stage 2–4 CRF evaluated; hypertension was found in 54% of patients and half of them did not respond to the treatment [12]. Due to the fact, keeping blood pressure in normal levels has been known to reduce and delay the risks of cardiovascular diseases. In our study, systolic and diastolic blood pressures in patients were found to be significantly higher than the control group but LVMI calculating was not considered.

Postmortem studies indicated that >50% of CRF patients had LVH [1,15]. Cardiovascular problems may occur due to vascular pathologies and LVH in patients with CRF. Previous studies have reported that LVH started in mild to moderate CRF and it progressed with the increasing level of kidney failure [16]. Most studies on this issue demonstrated different proportions of LVH and increase in LVMI. Among 29 children with stage 5 CRF, 69% had LVH and 83% had abnormal left ventricular geometry in pre-dialysis period [17]. In the two-year follow-up of 31 children with CRF, it was shown that the LVH incidence increased from 19% to 39% at the end of second year [13]. Probably, due to the smaller ages of the patients, IVSd and LVPWd diameters were similar in both groups in our study.

It has been known that preserved systolic functions and deterioration in diastolic functions have been detected in early stages of CRF. The studies suggested that systolic dysfunction may start after the years of diastolic dysfunctions [16,18]. The relation of diastolic dysfunction with volume overload has also been demonstrated [19]. Johnstone et al. [20] reported a decrease E/A ratio in CRF children. Atalay et al. [16] showed that systolic cardiac functions were in the normal range although there were left ventricular hypertrophy and diastolic dysfunction. Parallel with the literature, our results demonstrated that LVESD and EDV values indicating the volume overload were significantly higher in CRF group. Moreover, significant decrease in E/A value indicating diastolic dysfunction was also observed.

It has also been considered that different rates of arrhythmias were found in CRF patients. In a recent study, 575 patients with myocardial infarction were followed for 2 years and it was found out that ventricular tachyarrhythmia and death rate significantly increased correlated

Table 3
ECG information for CRF patients and control subjects.

	CRF n = 40	Control n = 47	p
V1 TWA (μV), mean ± SD	51.43 ± 13.56	49.52 ± 10.66	0.455
V5 TWA (μV), mean ± SD	55.03 ± 14.13	45.61 ± 13.75	**0.028**
AVF TWA (μV), mean ± SD	69.85 ± 22.31	52.42 ± 13.95	0.276
TWA in the highest lead (μV), mean ± SD	67.56 ± 40,65	50,33 ± 15.34	0.258
Isolated ventricular ectopic beats or couplets (%)	25,8	17.02	0.152
TWA <47 μV (n, %)	19 (47.5)	22 (46.81)	0.514
TWA >47 μV (n, %)	21 (52.5)	25(53.19)	0.309

CRF; Chronic renal failure, TWA; T-wave alternans.
Bold values indicate significance at $p < 0.05$.

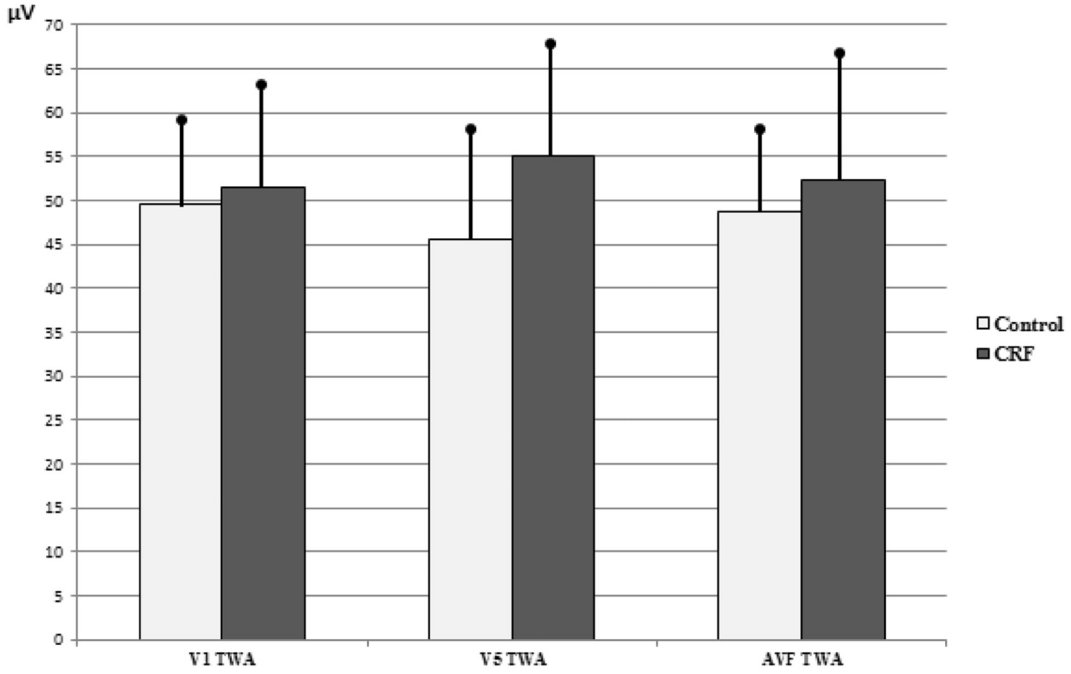

Fig. 1. Comparison of the maximum T-wave alternans values of chronic renal failure and control groups. V5 lead were significantly higher in patients with chronic renal failure ($p = 0.028$).

with positive Holter results [7]. In a multicenter study conducted in hemodialysis patients, the rates of ventricular arrhythmias detected as 76% where supraventricular arrhythmias 69% [21]. In this study, rates of arrhythmias were found out as 35% for the patients while most of whom were supraventricular (25%) and only 4 patients (10%) had ventricular arrhythmia. Probably, regarding the younger age of the population, our study had low rate of arrhythmia.

In the literature, the relationship between the risk of sudden cardiac death and TWA were evaluated in the patients with cardiomyopathy and myocardial infarction. Previous studies have demonstrated that TWA values increased after myocardial infarction and therefore the risk of sudden death increased. In an experimental study, the pigs of which left coronary arteries were occluded and myocardial infarction was created, TWA values were found to be increased [22]. Also, the relationship between TWA and ventricular arrhythmia as well as mortality and morbidity in patients with cardiomyopathy have been shown clearly. In a large study conducted in patients with idiopathic cardiomyopathy, the TWA values were positively correlated with low EF values and left ventricle enlargement [23]. In another study in dilated cardiomyopathy patients, ventricular arrhythmia was detected with positive TWA values (88%) [24].

In premature cardiovascular events, especially sudden cardiac death have commonly been observed in the CRF patients associated with uremic cardiomyopathy yet it has been difficult to identify the patients at high risk. Since the abnormality rate of microvolt TWA in CRF patients has increased, TWA evaluation has been applied to detect the ones at high risk in terms of ventricular tachyarrhythmias.

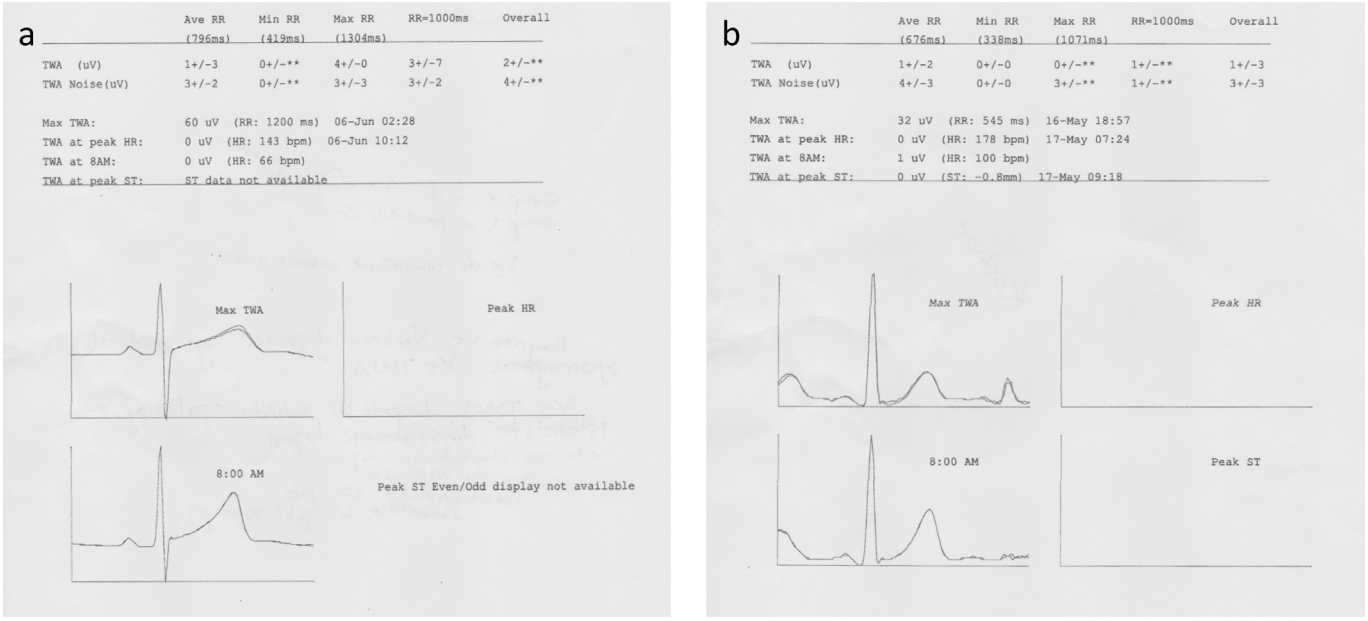

Fig. 2. T-wave alternans in a representative QRS aligned templates in chronic renal failure (a) and control patients (b).

In a single-center observational study reported by Patel et al. [8] 200 adult patients with end-stage renal disease (ESRD) and 30 patients with left ventricular hypertrophy were evaluated by means of cardiovascular history, ECG, cardiac MRI and microvolts TWA exercise tests. They found out abnormal microvolt TWA in 26.7% of patients with left ventricular hypertrophy and 57.5% in ESRD. These microvolt TWA abnormalities in ESRD patients were associated with uremic cardiomyopathy, clinical history of atherosclerosis (especially coronary, cerebral and peripheral), diabetes, older age and hemodialysis. In another study there was no significant increase in TWA of hemodialysis and peritoneal dialysis patients [25]. While microvolt TWA results seem to be conflicted with the adults, there are no studies in children with CRF. In our study, we have found out that TWA values in all derivations have increased in CRF patients and lead V5 values have been statistically significant. Makarov et al. [26] reported in the study related to the characteristics of TWA in children that maximal values of TWA were in lead V5 for 58 patients (86%), in lead V1 for 6 patients (9%) and in lead aVF for 4 patients (5%). A similar method was used in our study and maximum values and significant increase were detected in lead V5.

This study has had some strengths and limitations. The strength of our study is that it is prospective. Our study may fill an important gap in clinical knowledge of TWA, namely, characterization of TWA in children with CRF before development of significant left ventricular hypertrophy and arrhythmia and in normal controls matched for age and sex. As detailed analysis was not able to be made due to small number of patients when divided into subgroups, we did not evaluated microvolt TWA to predict cardiovascular events in children with CRF. In fact, TWA predicts cardiac mortality and sudden cardiac death in population studies and is not limited to patients with ischemic heart disease [27,28]. Unfortunately, the outcomes of long-term follow-up were not evaluated in the current study. In the light of our findings, further studies will be needed to answer this question. Data of microvolt TWA values in pediatric patients with CRF and controls enrolled in this study were surprisingly high. Similarly, Doksoz et al. have examined microvolt TWA in 24-h Holter ECG of children with repaired tetralogy of Fallot to assess associations of microvolt TWA with ventricular arrhythmias, ECG parameters, and echocardiographic findings [29]. They found that median microvolt TWA was 95.5 μV in the study group and the median MTWA in the control group was 55.5 μV.

Conclusions

In conclusion, our study has demonstrated that microvolt TWA values increased in pediatric patients with CRF. In the future, TWA can probably be used for early risk assessment in pediatric patients with CRF. Prospective, long-term studies with a large number of patients are required to determine the cut-off values of microvolt TWA and understand the relationship with mortality and long-term follow-up.

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Statement of ethics

The research was ethically conducted in accordance with the World Medical Association Declaration of Helsinki. We declare that the parents of the subjects were informed and written consent was obtained, and the study protocol was approved by an appropriate ethics committee: Mersin University Ethics Committee approved this study (2012/66).

Conflict of interest

None.

Financial disclosure

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