Microvolt T-Wave Alternans during Holter Monitoring in Children and Adolescents

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Background: Time-domain microvolt T-wave alternans (TWA) has been described as a noninvasive marker of sudden cardiac death in adults. The incidence of TWA in pediatric populations has not been defined well. The aim of the study was to determine peculiarities of TWA in children.

Methods: We examined 68 healthy patients—newborns (20) and children in age group of 7–17 years (48)—and 85 pediatric patients: ventricular premature beats—65; dilated cardiomyopathy (DCMP)—2; long QT syndrome (LQTS)—10; Brugada syndrome (BrS)—5, catecholaminergic ventricular tachycardia (CVT)—3. All underwent Holter monitoring (HM) with definition of the peak value of TWA by modified moving average method.

Results: In healthy newborns, TWA was 32 ± 8 (12–55) μV (HR 123–156 bpm). In healthy children (7–17 years) it was 30 ± 11 (10–55) μV (HR 64–132 bpm) without any differences between boys and girls. In all group of patients, TWA were significantly higher ($P < 0.05$) than in healthy. Circadian peak of TWA was found (90%) in a second part of day and at sleep (8%). Among them 60% (LQTS, BrS, and DCPM) had TWA $> 55 \mu\text{V}$.

Conclusion: Time-domain TWA during HM in children was independent of age, gender, and heart rate. In 94% healthy children, values of TWA do not exceed 55 μV but 20–50% children with cardiac pathology had TWA more than 55 μV . Night circadian type of TWA in diseases with risk of life-threatening arrhythmias associated with TWA was more than 55 μV .

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T-wave alternation is the change of amplitude, morphology, and polarity of the T wave in several subsequent electrocardiographic complexes. Visible or so-called macroscopic T-wave alternation for the first time has been described about 100 years ago by Hering¹ and Lewis.² Later, it was reported as visible T-wave alternation in adult patients with various cardiac diseases—myocardial ischemia,³ vasospastic angina,⁴ electrolyte abnormalities,⁵ dilated cardiomyopathies,⁶ life-threatening arrhythmias,^{7,8} and long QT syndrome.⁹ In a pediatric population, visible T-wave alternation has been described in children with inherited long QT syndrome.^{9–11}

Visible T-wave alternation assessment is very subjective approach with numerous limitations and a method of automated evaluation of microvolt T-wave alternation during exercise testing or atrial

pacing (Conventional Spectral based method or Cambridge Heart method) was developed later and the presence of it was associated with the high-risk of ventricular tachycardia.^{12,13} Unfortunately, routine clinical application of spectral method is limited. Since exercise testing or atrial pacing is difficult to perform in some group of patients (severe heart failure, early period after myocardial infarction, age limitation for stress test, or atrial pacing), special expensive electrodes to lower noise must be used. Recently, time-domain method analyses of microvolt T-wave alternation was proposed by Verrier et al.¹⁴ who possibly used the commercially available modified moving average (MMA) method. The use of MMA for ambulatory microvolt T-wave alternation testing is currently limited in pediatric population because of the absence of normal limits and established diagnostic criteria.

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The aim of our study was to determine normal limits of the microvolt T-wave alternation detected by MMA method in healthy children and its peculiarities in patients (children) with cardiovascular diseases.

Patients

This study comprised 80 (42 boys and 38 girls) apparently healthy children in age group of 0–17 (8.2 ± 6.1), 20 (14 boys and 6 girls) healthy newborns at 1st, 2nd, and 4th day after birth, and 60 (28 boys and 32 girls) children and adolescents in age group of 7–17 (10 ± 4.1). The inclusion criteria for healthy newborns were: normal pregnancy and delivery, healthy mother aged 18–28; gestational age of a baby at birth 38–40 weeks; body mass at birth ≥ 2700 grams; Apgar scale ≥ 8 , absence of cardiovascular pathology at physical examination, and rest 12-lead ECG. The healthy children in 7–17 age group were selected for study from consecutive pediatric prophylactic medical examination based on the absence of cardiovascular pathology at routine clinical evaluations, including physical examination, blood pressure measurements, and 12-lead ECG showing no cardiac disease.

Eighty-five children, in 7–17 (11.8 ± 4.5) age group, were also examined for cardiovascular pathology—65 with ventricular premature beats (VPB) without structural or congenital heart diseases, two with dilated cardiomyopathy (DCMP), 10 with inherited long QT syndrome (LQTS), five with Brugada syndrome (BrS), and three with catecholaminergic polymorphic ventricular tachycardia (CPVT).

The study protocol was approved by the ethics committee of Clinical Children Hospital #38 of Federal Medical-Biological Agency of Russia. Informed consent was given by parents of all healthy children.

Holter ECG Monitoring and Measurement of Microvolt T-Wave Alternans

All participants underwent 24-hour Holter ECG monitoring (HM) performed using digital recorders Seer MC, GE Medical systems (GE Healthcare Inc., Milwaukee, WI, USA) in three leads (V_5 , V_1 , and aVF). The sampling rate was 128 Hz. Analysis of the microvolt T-wave alternans (TWA) was performed by time-domain MMA using software Mars PC system, version 7.5 with definition of the peak value of TWA. TWA was analyzed in modified leads V_5 , V_1 ,

and aVF from routine 24-hour HM. The maximal TWA voltage at a heart rate less than 160 bpm was derived automatically in three leads. After that, manual editing was performed if the data were not available for analyses due to noise or artifacts. The system displayed maximal time-domain TWA magnitude on the screen and the highest values of TWA in the three leads was chosen for assessment.

Statistics

We completed data statistical analysis with non-parametric methods using Statistica for Windows (StatSoft, Tulsa, OK, USA), version 7. Normally distributed data were expressed as mean $\pm$ standard deviation ($m \pm SD$) and 5–95%. Student's *t*-test and Wilcoxon matched-pairs test were used for comparison where appropriate. Correlation was expressed as Pearson's correlation coefficient. A *P* value lower than 0.05 was considered significant.

RESULTS

Twelve healthy children in 7–17 age group were excluded from the analysis because in the figures of peak TWA odd and even beat templates do not line up in T-P segment or P-wave, or QRS complex, so we considered that as artifact. In healthy newborns, the values of TWA were $32 \pm 8 \mu V$, from 12 to $55 \mu V$ (5 and 95%, accordingly), and they registered the heart rate between 123 bpm and 156 bpm. The values of TWA in healthy group of 7–17 years of age were revealed in heart rate between 64 bpm and 132 bpm ($P < 0.05$ from newborns) and were established as $30 \pm 11 \mu V$, from 10 to $55 \mu V$ (5–95 %). The highest maximal values of TWA were revealed in modified lead V_5 in 58 (86%) children, lead V_1 in 6 (9%), and lead aVF in 4 (5%) children.

There were no differences between boy and girl in the TWA values. The mean average TWA in all groups of children with cardiovascular diseases was significantly higher than in healthy children (Table 1).

We did not find any difference in heart rate when TWA was registered in children with cardiovascular pathology and healthy (56–137 vs. 64–132 bpm, respectively). There was a strong correlation between the longest QT interval and the peak value of TWA, $r = 0.46$; $P < 0.05$ (Fig. 1).

Table 1. The Value of Microvolt TWA in Healthy Children and Pediatric Patients with Cardiovascular Pathology

Subjects	N	Age M ± SD	TWA (μV) M ± SD	5–95% (μV)	>55 μV n (%)	P From Healthy
Healthy	48	10 ± 4.1	30 ± 11	10–55	3 (6)	—
VPB	65	12.1 ± 4.3	45 ± 23	15–98	14 (21)	P < 0.005
DCMP	2	12	68 ± 43	37–99	1 (50)	P < 0.0001
LQTS	10	11.6 ± 3.9	48 ± 20	19–80	4 (40)	P < 0.0001
BrS	5	11.5 ± 7	39 ± 28	10–86	1 (20)	P < 0.005
CPVT	3	12.3 ± 3.2	49 ± 11	39–60	1 (33)	P < 0.05

VPB = ventricular premature beats; DCMP = dilated cardiomyopathy; LQTS = long QT syndrome; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia.

We also analyzed two additional criteria—circadian pattern of TWA and location of maximal voltage of TWA on JT segment (from the J point to the end of the T wave). Comparing the time of registration between the circadian peak TWA values in 94% healthy children and 92% patients with cardiovascular diseases, we found it was mostly present during a wakeful state previously at second part of day period (Fig. 2).

Heart rate for night circadian type of peak value of TWA ranged from 64 to 108 bpm. In three (6%) healthy children and seven (8%) patients with cardiovascular pathology the circadian peak, TWA was registered during sleep (Table 2). Among them, 40% (two healthy children and three patients with VPB) had maximal TWA values less than 55 μV

and 60%—one healthy children, two LQTS patients with LQT3 mutation, one with DCPM, and one patient with BrS (Fig. 3)—had TWA more than 55 μV.

Location of maximal voltage TWA on T wave (Fig. 4) was mostly found at the ascending part of the T wave (92% of cases, type A, Fig. 4A) and in limited cases on the top of the T wave (4%, type B, Fig. 4B), on the ST segment (3%, type C, Fig. 4C),

Figure 1. Relationship between the peak value of TWA and the longest QT interval during Holter monitoring in 48 healthy children in 7–17 years of age. Correlation 0.46, $P < 0.05$.

Figure 2. (A) Circadian rhythm of the peak value of time domain TWA in 48 healthy children in 7–17 years of age (circadian peak of TWA at 6 PM). (B) Circadian rhythm of the peak value of TWA in 85 children with cardiovascular diseases (circadian peak of TWA at 2–4 PM).

Table 2. Characteristics of Children with Night Circadian Type of TWA

Subjects	Diagnosis	Age	Sex	Circadian Peak of TWA	TWA (μ V)	RR TWA (msec)
1	Healthy	12	M	05:29	26	681
2	Healthy	10	M	01:14	98	857
3	Healthy	9	M	04:36	24	937
4	VPB	7	M	03:52	49	821
5	VPB	15	M	02:07	41	909
6	VPB	17	M	03:24	41	857
7	LQTS (LQT3)	8	M	05:43	73	1052
8	LQTS (LQT3)	13	M	03:56	80	625
9	DCMP	12	F	01:03	99	869
10	BrS	17	M	05:28	86	1000

VPB = ventricular premature beats; LQTS (LQT3) = long QT syndrome (3rd genotype); DCMP = dilated cardiomyopathy; BrS = Brugada syndrome.

and at the descending part of the T wave (1% of cases, type D, Fig. 4D).

DISCUSSION

Early TWA has been described as a noninvasive marker of life-threatening ventricular arrhythmia in some adult cardiac populations. The incidence and potential significance of TWA in pediatric populations has not been defined well. In a study by Cheung et al.¹⁵ TWA was evaluated by spectral method during bicycle exercise test in 100 apparently healthy children in an age group similar to our study (from 8 to 17 years old). There was no significant difference between age, gender, endurance, maximum heart rate, QRS duration, QT, or QTc interval in children with and without sustained TWA that was present in 11% of normal children, but was absent at heart rates below 120 bpm

and rare (1.2%) below 60% of predicted maximum heart rate. Alexander et al.¹⁶ studied spectral TWA in 304 pediatric patients with heart disease and symptoms (congenital heart disease, myopathy, potential myocardial ischemia, syncope, or history of cardiac arrest) by a treadmill exercise test. Abnormal TWA was registered in 24 (7%) patients including 19 with high risk for serious events (three of them had cardiac arrest). Authors concluded that pathologic values of sustained TWA is associated with high risk of serious events in pediatric patients while the absence of TWA has relatively high negative predictive value, but it does not completely exclude the potential for serious sustained ventricular arrhythmias. Both studies were performed by spectral-based method. We have not found data about results of TWA assessment by time-domain MMA algorithm in children.

A several retrospective^{17–19} and prospective^{20,21} studies were performed by MMA method in adult

Figure 3. Night circadian peak of TWA in Brugada syndrome (17-year-old patient). (A) ECG pattern of Brugada syndrome; (B) maximal peak value of TWA 86 μ V at 5:28 AM in modified lead V₁.

Figure 4. The types of pattern location of point of maximal voltage of TWA on JT segment in children in modified lead V_5 . (A) segment ST + ascending part of T wave (92%); (B) the peak of the T wave (4%); (C) segment ST (3%); (D) descending part of T wave (1%).

population. In the study by Sakaki et al.²¹ authors used a cutoff point of TWA higher $65 \mu\text{V}$ that was significantly associated with cardiac mortality in adult population. In this study, the mean values of TWA in patients with and without the primary end-point (cardiac arrest) were 72 ± 20 and $52 \pm 15 \mu\text{V}$, respectively. But the cutoff value of $65 \mu\text{V}$ was higher than of other previous study,¹⁷ which was assessed by time-domain MMA method (46.6 and $53 \mu\text{V}$ in V_1 and V_5 , respectively). For our results, time-domain TWA on 24-hour HM did not exceed $55 \mu\text{V}$ in both the age groups of healthy children (newborns and children and adolescents of 7–17 years of age). Nieminen et al.²⁰ obtained $39 \pm 19 \mu\text{V}$ as the mean value of TWA by MMA method in surviving adult patients during exercise test. It was very similar to our mean value of TWA in the group of healthy children. This result and absence of difference in age and gender in our healthy group allow us to speculate that value of time-domain TWA may be a universal marker of electrical heart condition. We obtained close relation of TWA to longest QT interval during HM (Fig. 1), probably because both parameters reflected electrical instability of heart.

In our observation, the magnitude of time-domain TWA was significantly higher in all groups of cardiac disorder compared to with healthy children and the highest in the nonischemic DCM

patients ($68 \pm 43 \mu\text{V}$). Previous studies on adult patients also revealed that the magnitude of time-domain TWA in patients with nonischemic DCM and left ventricular dysfunction was higher than in patients with ischemic left ventricular dysfunction.²¹

It is well known that children with LQTS have very high risk of sudden cardiac death. Diagnosing congenital LQTS is difficult due to variable penetrance and genetic heterogeneity. Accurate diagnosis is made difficult by limitations of the ECG as a diagnostic tool, because the QT intervals of affected and unaffected individuals overlap substantially. In a study by Kaufman et al.²² 49 family persons from 101 genotyped members of a family with LQTS, including 26 carriers of the KCNH_2 (HERG) mutation, underwent history, ECG analysis, 24-hour HM with QT, and heart rate variability analysis exercise testing with QT analysis and spectral TWA. QTc was not helpful as a discriminator in carrier children less than 13 years of age. Among genetically affected family members, 18% had abnormal TWA during exercise test. None of the genetically unaffected members had abnormal TWA. Microvolt TWA had high specificity (100%) but was an insensitive (18%) marker for LQTS carrier.

There were a few data about circadian rhythm of TWA. Analysis of circadian dispersion of maximal TWA values in our groups showed that most

cases of TWA develop during second part of diurnal period. Eight percent of children from 133 healthy and sick children demonstrated night circadian peak of TWA (Table 2). Forty percent of them were patients with inherited diseases with high risk of sudden cardiac death—DCMP, LQTS (LQT3 genotype), and BrS which had value of TWA more than $55 \mu\text{V}$. It is known that BrS and LQTS are syndromes with risk of fatal events predominantly during the night/sleep period.^{23,24}

We have revealed different patterns of maximal voltage TWA on T wave. Typical was localization on the ascending part of the T wave, but in few cases there were other localizations (Fig. 4). Some authors mentioned that different parts of the T wave on ECG reflect transmural, transseptal, and apico-basal heterogeneities of final repolarization of the action potential within ventricular myocardium that may be responsible for pattern and inscription of the T wave.^{25–27} Full repolarization of the epicardial action potential is coincident with peak of the T wave, and repolarization of the M cells coincides with the end of the T wave and determines the QT interval prolongation. The interval between the peak and end of the T wave (Tpeak-Tend) has been suggested to provide an index or marker of transmural dispersion of repolarization, which may be useful for assessment of patients with risk of life-threatening arrhythmias.^{28,29} Based on our results, we can speculate that definition type of the maximal voltage TWA on T wave during HM may be perspective for clinical assessment condition of heterogeneities ventricular repolarization especially in patients with inherited arrhythmias and channelopathies.

Study Limitations

We have no possibility to compare our results to previous studies that assessed by time-domain method TWA during HM in children and to other noninvasive markers, including spectral TWA. Only a few children with inherited channelopathies molecular genotype identification have been available. The number of patients in some group of this study is relatively small and some of them have been taking antiarrhythmic drugs. We had short period of the follow-up, which did not make possible to determine the outcomes in the our clinical groups and to determine the cutoff of points for TWA in the children.

Conclusion

- (1) Assessment of the time-domain TWA during 24-hour Holter ECG monitoring would be useful for screening in pediatric patients at any age.
- (2) Values of the time-domain TWA during 24-hour Holter ECG monitoring in healthy children independent of age, gender and level of heart rate.
- (3) In healthy children, the peak values of the time-domain TWA during 24-h Holter ECG monitoring do not exceed $55 \mu\text{V}$ in 94% but for children with cardiovascular pathology TWA more than $55 \mu\text{V}$ revealed in 20–50%.
- (4) Night circadian type of TWA in children with inherited diseases with risk of life-threatening arrhythmias was associated with values of the time domain TWA more than $55 \mu\text{V}$.

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