Increased microvolt T-wave alternans in children and adolescents with Eisenmenger syndrome

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Abstract

Objective: To determine the values of microvolt T-wave alternans (MTWA) in children and adolescents with Eisenmenger syndrome (ES) and controls.

Methods: Thirteen were included in the study. After analyzing the 24-h ECG recordings, MTWA was considered using three leads (V5, V1, and aVF). Right heart catheterization and 6-minute walk test (6-MWD) were applied to the patients and pro-brain natriuretic peptide levels were assessed; echocardiographic parameters were obtained from both the groups and the results were compared.

Results: The MTWA value in lead V5 was 81.08±10.73 μV in the patient group (63.50±18.78 μV in the control group), in lead V1 was 75.00±16.86 μV (73.94±16.77 μV in the control group), and in lead aVF was 73.77±17.81 μV (72.61±16.21 μV in the control group). Comparison of MTWA values between patients and controls revealed that only lead V5 values were statistically different in the ES group. The 6-MWD scores significantly correlated with lead V5. Right atrial volume and right ventricular fractional area change were significantly correlated with lead V1. The Tei index was significantly correlated with lead aVF.

Conclusion: The MTWA lead V5 value was significantly higher in children with ES than in controls and was also correlated with decreased exercise tolerance. *(Anatol J Cardiol 2018; 19: 303-10)*

Keywords: arrhythmia, Eisenmenger syndrome, echocardiography, microvolt T-wave alternans

Introduction

Pulmonary arterial hypertension (PAH) is characterized by progressive and devastating disease with poor prognosis (1). Structural, mechanical, and electrical remodeling in the right ventricle leads to increased risk of arrhythmia event (2-4). ECG changes in patients with PAH are well known; however, the effects on the ECG change in PAH therapy are still unclear. There are limited studies (1, 2) about noninvasive tests to determine the risk of ventricular arrhythmias and sudden cardiac death in adults with PAH. Microvolt T-wave alternans (MTWA) are known as noninvasive predictors of ventricular arrhythmias in patients with cardiomyopathies (5, 6). Although there are some limited studies (7, 8) regarding MTWA in children, there is no study in children with Eisenmenger syndrome (ES). Hence, the aim of this study was to determine the MTWA values in children with ES compared with the controls and correlate the values with echocardiographic and clinical parameters.

Methods

Thirteen patients with ES and 18 healthy children matched by sex and age (range, 3–21 years) were included. Among the 13 patients, 9 were diagnosed with PAH associated with ES due to ventricular septal defect and four with atrioventricular septal defect. The patients were diagnosed based on the current the European Society of Cardiology and the European Respiratory Society and the American Society of Echocardiography guidelines for the diagnosis and treatment of pulmonary hypertension (PH) (9, 10). All these patients were followed up in the cardiology clinics for approximately 53 months before the study. Two of the patients (15.4%) were New York Heart Association (NYHA) functional class 2 and the others (84.6%) were class 3. Three patients had a history of syncope. All patients were receiving PAH-specific treatment (bosentan, sildenafil, or tadalafil). The control group comprised 18 healthy individuals with no physical examinations and history of cardiovascular disease. Exclusion criteria

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were congenital and valvular heart disease, cardiomyopathies, systemic hypertension, and arrhythmias. Written informed consent was obtained from the parents as well as children (under 18 years old), if possible. The Institutional Ethics Committee approved the study.

Right heart catheterization

The diagnosis of PH was made by right heart catheterization. Mean pulmonary arterial pressure (mPAP), systolic pulmonary arterial pressure (sPAP), capillary wedge pressure, and pulmonary vascular resistance were measured. PH was defined by a resting mPAP of ≥25 mm Hg, pulmonary vascular resistance index of >3 WU.m^2 (9, 10). Right heart catheterization was not performed in the control group.

Echocardiography

The patient and control groups were evaluated using transthoracic echocardiography (TTE) (Vivid S5 Pro Ultrasound System; GE Medical Systems, Horten, Norway) using 3 and 6 MHz transducers. The left ventricle ejection fraction (LVEF) was calculated using the Simpson's biplane method. All echocardiographic measurements were performed according to the current guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging (9, 10). Systolic pulmonary arterial pressure (sPAPecho) was considered equal to the right ventricular (RV) systolic pressure in the absence of RV outflow tract obstruction or pulmonary stenosis (PS). sPAPecho was determined from the peak tricuspid regurgitant velocity as recommended using the modified Bernoulli equation considering the right atrial (RA) pressure gradient. The RA pressure was calculated from the diameter of the inferior vena cava and its response to inspiration (10). Right ventricle morphology was defined using the following parameters: RV end-diastolic area (RVEDA), RV end-systolic area (RVESA), RV end-diastolic diameter (RVEDD), and RV free wall thickness (RVWT). RVWT was measured in a diastole from the subcostal view using M-mode imaging. RVEDD was measured as the maximal short-axis dimension in the basal one third of the right ventricle at end-diastole from a right ventricle-focused apical 4-chamber view. In addition, certain parameters were measured using RV performance, tricuspid annular plane systolic excursion (TAPSE). RV fractional area change (RVFAC) was calculated as the difference of RVEDA and RVESA and the ratio of RVEDA multiplied by 100. Isovolumic relaxation time (IVRT), peak systolic velocity of the lateral tricuspid annulus (S't), and Tei index were measured using pulsed wave tissue Doppler imaging. Right atrial volume (RAV) was also obtained.

Clinical evaluation

The NYHA functional class was based on the patients' history. Functional capacity was measured using the 6-minute walk distance (6MWD), which was evaluated in a standardized manner in an indoor 50-m corridor. The transcutaneous oxygen saturation (tcSO2) values of the patients were measured using handheld pulse oximeter placed on the index finger of the patient's right hand before and during the 6-minute walk test (6MWT) (11). In addition, pro-brain natriuretic peptide (BNP) levels were measured using Immulite 2000 immunoassay system (DPC, UK) in all patients. The principle of procedure of proBNP is a solid-phase two-site chemiluminescent immunometric assay (Cat number: L2KNT2).

Holter ECG and microvolt T-wave alternans measurement

A digital recording device, Seer MC (GE Medical Systems, Nogoya, Japan), was attached to the subjects for 24-h Holter electrocardiography (ECG) monitoring, and a sampling velocity of 128 Hz was selected. In both groups, the recordings were obtained in sinus rhythm. In the patient group, the prescribed drugs were continued throughout Holter ECG monitorization. Microvolt T-wave alternans analysis was performed in the form of maximum MTWA analysis using the Mars PC system software, 7.2 version. The time domain of modified moving average (MMA) was used for analysis. Microvolt T-wave alternans was analyzed from routine 24-h Holter ECG recording based on the V5, V1, and aVF leads.

Statistical analysis

Power analysis was calculated according to baseline PO2 and the effect size detected as 15.6, with 90% power and 5% alpha type one error (1). The sample size was found as minimum nine patients in each group. The data are presented as mean ± standard deviation and the values of frequency. For categorical independent variables, Fisher's exact test was used for comparison of the groups in terms of outcome variables. The normality of the continuous variables was assessed by the Shapiro–Wilk test, and the groups were compared using the independent t-test and Mann–Whitney U test (25%–75%). Correlations between the continuous measurements were evaluated using the Pearson and Spearman's rank correlation coefficient. The data were analyzed using STATA/multiprocessor computers (STATA /MP11-StataCorp LP 4905, Lakeway Drive College Station, TEXAS-77845) package program, and a p-value of <0.05 was considered statistically significant.

Results

The demographic and clinical data of the study population is presented in Table 1. The mean age of the patients was 14.3±5.5 years. No difference was found between the patient and control groups regarding diastolic blood pressure, whereas the systolic blood pressure was significantly lower in the patient group than in the control group (99.62±7.21 and 108.89±7.39 mm Hg, respectively; p=0.002). The mean heart rate was higher in patients than in controls (90.92±11.85 and 80±13.95 bpm, respectively ; p=0.03). The left ventricular ejection fraction was within the normal range in both groups. The left ventricular (LV) eccentricity index was

Table 1. Demographic, clinical, and echocardiographic left ventricular parameters

	Patients (n=13)	Controls (n=18)	*P*
Age (year)	14.31±5.54	13.11±2.70	0.482
Female (n/%)	10 (76.9%)	12 (66.7%)	0.696
HR (bpm)	90.92±11.85	80.00±13.95	0.030
Syst. BP (mm Hg)	99.62±7.21	108.89±7.39	0.002
Diast. BP (mm Hg)	65.92±7.87	69.44±6.39	0.180
proBNP (pg/mL)	242.94±178.21	-	-
6MWD (m)	271.85±77.01	-	-
LVEDD (mm)	34.08±7.29	40.72±3.41	0.008
LVESD (mm)	21.38±5.41	24.83±1.62	0.043
EF (%)	68.46±6.23	70.89±2.61	0.205
LVEI	0.57±0.12	0.81±0.05	<0.001

BP - blood pressure; BNP - brain natriuretic peptide; Diast - diastolic; HR - heart rate; Syst - systolic; 6MWD - 6-minute walk distance; LVEDD - left ventricular (LV) end-diastolic diameter; LVESD - LV end-systolic diameter; LVEF - LV ejection fraction; LVEI - LV eccentricity index

found to be significantly higher in the patient group (0.81±0.05 and 0.57±0.12, respectively; p<0.001).

RVEDD, which shows RV dilatation, was significantly higher in the patient group (p<0.001), whereas RVEDA and RVESA were also larger in the patient group, although they were not statistically significant. RAV was significantly larger in the patient group than in the control group (p=0.001). The change in RVFA was lower in the patient group, but it was not statistically significant (p=0.108). However, similar values for TAPSE, pulmonary arterial acceleration time (PAAT), and S't were observed in the patient group, which were significantly lower than those in controls (p<0.001 for all). The Tei index, RVWT, and IVC diameter were found to be significantly higher in the patient group (p=0.003, p<0.001, p<0.001, respectively). The morphological and functional RV echocardiographic parameters are shown in Figure 1.

Examination of the patients' Holter ECG recordings did not reveal severe arrhythmia. The MTWA value in lead V5 was 81.08±10.73 μV in the patient group (63.50±18.78 μV in the control group), in lead V1 was 75.00±16.86 μV (73.94±16.77 μV in the control group), and in lead aVF was 73.77±17.81 μV (72.61±16.21 μV in the control group). Comparison of the MTWA values between the patients and controls showed that only lead V5 values were statistically increased in the PAH group (p=0.003) (Fig. 2). A sample of QRS-aligned templates of the patient and control is shown in Figure 3. The MTWA values were compared using the parameters that showed the morphology and function of the right ventricle with the tests that reflected clinical status. Lead V5 was found to be significantly correlated only with 6-MWD (r=0.623, p=0.023). Lead V1 was found to be correlated with RAV and RVFAC (r=–0,717, p=0.006, r=0.643, p=0.018, respectively). The lead aVF was found to be correlated with the Tei index (r=–0.595, p=0.032). The MTWA results are demonstrated in Table 2.

Table 2. Correlations between MTWA values and right ventricular parameters, proBNP, and 6-minute walk distance

Patients	LeadV5		LeadV1		LeadaVF	
	P	r	*P*	r	*P*	r
ProBNP (pg/mL)	0.368	0.272	0.556	0.180	0.172	0.403
6MWD (m)	0.023	-0.623	0.134	-0.438	0.185	-0.392
PAAT (ms)	0.209	-0.373	0.528	-0.193	0.761	0.093
TAPSE (mm)	0.446	0.236	0.588	0.700	0.549	-0.310
RVEDD (mm)	0.337	0.290	0.820	0.070	0.788	-0.082
RVEDA (cm^2)	0.875	-0.049	0.107	-0.468	0.298	-0.313
RVESA (cm^2)	0.578	-0.170	0.060	-0.534	0.431	-0.240
RVWT (mm)	0.943	0.299	0.156	-0.073	0.544	-0.141
RV/LV	0.459	0.225	0.326	0.295	0.832	-0.065
RAA (cm^2)	0.169	-0.406	0.006	-0.717	0.799	-0.782
S't (cm/sec)	0.162	0.680	0.070	0.383	0.086	0.246
Tei index	0.467	-0.335	0.202	-0.309	0.032	-595
TY (m/s)	0.566	0.175	0.574	0.171	0.333	0.291
RVFAC (%)	0.435	0.237	0.018	0.643	0.372	0.270
LVEI	0.749	0.098	0.161	0.412	0.079	0.503

BNP - brain natriuretic peptide; 6MWD - 6-minute walk distance; PAAT - pulmonary arterial acceleration time; TAPSE - tricuspid annular plane systolic excursion; RVEDD - right ventricular (RV) end-diastolic diameter; RVEDA - RV end-diastolic area; RVESA - RV end-systolic area; RVWT - RV wall thickness; RV/LV - right ventricular/left ventricular; RAA - right atrial area; S't - peak systolic velocity of the lateral tricuspid annulus; TY - Tricuspid regurgitation; RVFAC - RV fractional area change; LVEI - LV eccentricity index

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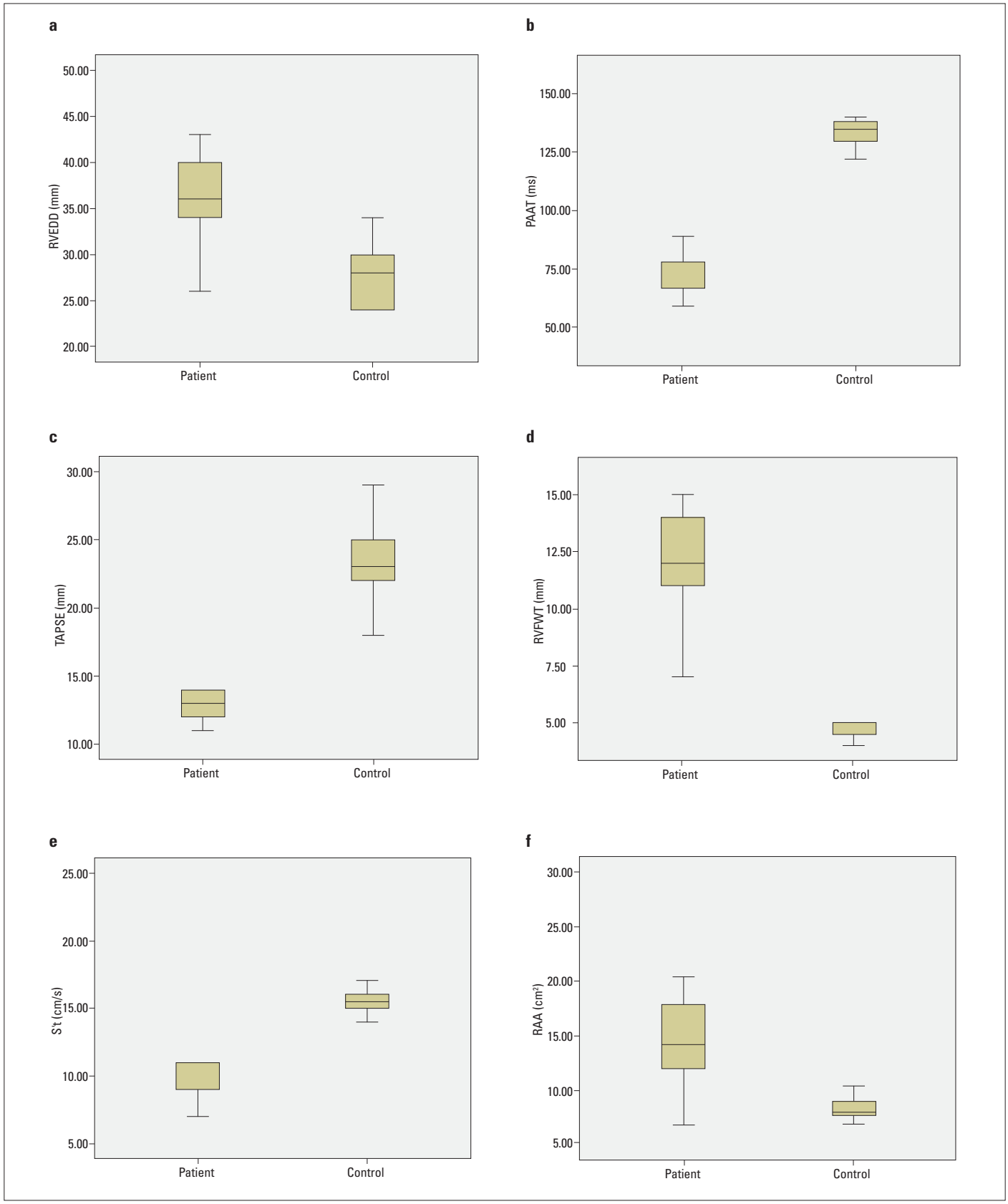

Figure 1. Graphic representation of echocardiographic-derived RV functional parameters. (a) RVEDD, right ventricular (RV) end-diastolic diameter. (b) PAAT, pulmonary arterial acceleration time. (c) TAPSE, tricuspid annular plane systolic excursion. (d) RVWT, RV wall thickness. (e) S't, peak systolic velocity of the lateral tricuspid annulus. (f) RAA, right atrial area

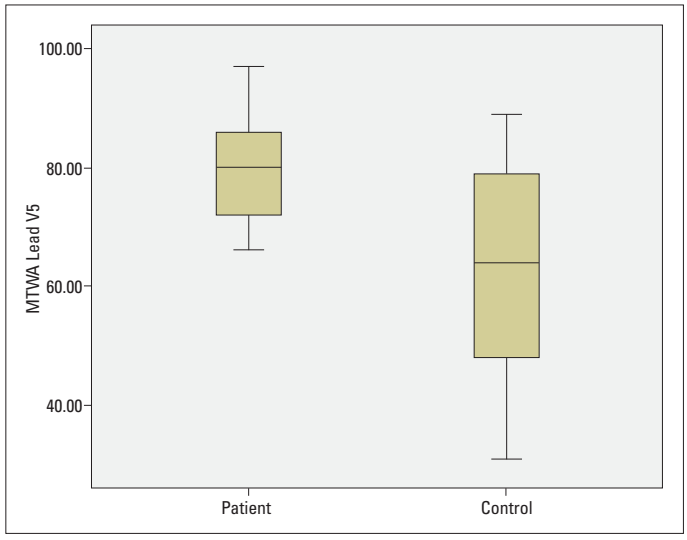

Figure 2. Lead V5 values statistically increased in PAH group (p=0.003)

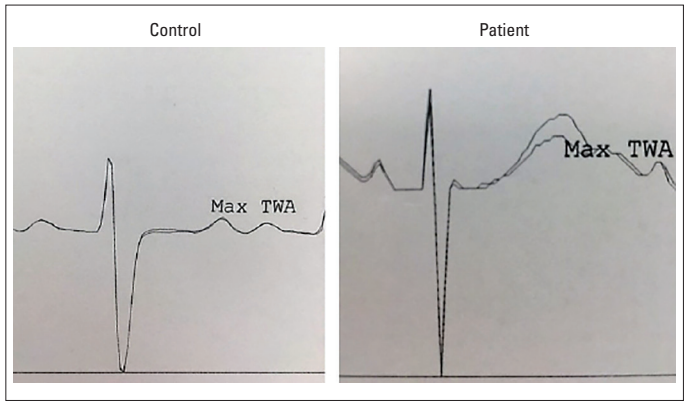

Figure 3. Figure of a QRS-aligned templates of the patient and control

A negative correlation was found between proBNP levels and TAPSE (r=–0.616, p=0.025). There was a negative correlation between 6-MWD and S't (r=–0.554, p=0.049) (Table 3). TcSO2 levels during 6MWT (85.62%±7.11%) were significantly lower than those before the test (76.23%±14.29%) (p=0.036).

Discussion

In this study, MTWA values were found to be increased in all three leads in the ES patient group, but were statistically significant only in lead V5. Lead V5 was negatively significantly correlated with 6-MWD.

The effect of vascular damage on RV functions is the most important factor that determines the survival and quality of life in PAH (12). In our study, a significant increase in RVWT was found in children with ES, which is compatible with the literature. RV performance gradually decreases, especially in PAH related with CHD. Giusca et al. (13) compared right ventricular morphologies and functions with PH types using echocardiographic imaging and found RVWT to be higher in the ES group than in the other groups, whereas RFAC and RV free wall strain values were better. The fact that the survival was better in ES patients associated with better functional capacity because of shunt. Better results in the presence of PFO in patients with IPAH also support this hypothesis (14). Echocardiographic studies conducted in recent years have also demonstrated that the RV short-axis functions in ES patients seem to be better than that in other PAH patients (15). Besides RVFAC, which reflects right ventricular function, was similar to the control group; a significant dilatation in the right ventricle and right atrium was observed in the patient group. Thus, it was assumed that lack of significant change in RVFAC despite a significant change in the right ventricular morphology might be explained with chronic exposure to shunt related with congenital heart disease.

Structural, mechanical, and electrical remodeling in the right ventricle and right atrium related with long-term increase in pressure and volume has been determined as the mechanism of arrhythmia in ES patients (1-4). Folino et al. (1) showed the presence of high density ventricular ectopy (premature ventricular contraction burden >700/24 h) with ambulatory ECG monitoring and a decrease in heart rate variability in four of nine PAH patients. Moreover, the risk of ventricular arrhythmia increases in these patients because of RV subendocardial ischemia, increased coronary perfusion pressure gradient and excessive RV load.

The mechanism underlying prolonged QTc and increased QTc dispersion in clinical arrhythmia in PAH patients and potential

Table 3. The correlation of proBNP and 6MWD between right ventricular parameters

Patiens	Pro BNP		6MWD	
	P	r	*P*	r
TY (m/s)	0.401	0.254	0.791	-0.080
PY (m/s)	0.748	0.098	0.808	-0.074
PAAT (ms)	0.354	-0.280	0.210	0.372
TAPSE (mm)	0.025	-0.616	0.500	-0.160
RVEDD (mm)	0.105	-0.470	0.460	0.224
RVEDA (cm^2)	0.596	-0.162	0.174	0.401
RVESA (cm^2)	0.760	-0.094	0.119	0.455
RVWT (mm)	0.336	-0.299	0.863	-0.181
RV/LU	0.602	0.159	0.181	-0.395
RAA (cm^2)	0.925	0.029	0.353	0.280
S't (cm/sec)	0.534	0.086	0.049	-0.554
Tei	0.520	-0.473	0.564	0.043
RVFAC (%)	0.524	0.194	0.210	-0.372
LVEI	0.494	0.208	0.507	-0.202

TY - tricuspid regurgitation; PY - pulmonary regurgitation; PAAT - pulmonary arterial acceleration time; TAPSE - tricuspid annular plane systolic excursion; RVEDD - right ventricular (RV) end-diastolic diameter; RVEDA - RV end-diastolic area; RVESA - RV end-systolic area; RVWT - RV wall thickness; RV/LV - right ventricular/left ventricular; RAA - right atrial area; S't - peak systolic velocity of the lateral tricuspid annulus; RVFAC - RV fractional area change; LVEI - LV eccentricity index

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predisposing factors have not yet been investigated in detail. It is known that the major cause of morbidity and mortality in patients with ES is cardiac arrhythmias. In recent years, MTWA, a noninvasive method, is used in patient groups indicating the risk for sudden cardiac death. MTWA is an electrocardiographic (ECG) phenomenon displaying inhomogeneity of the myocardial repolarization process. The prognostic value of MTWA in ischemic heart diseases, heart failure, and cardiomyopathies has been demonstrated (16-19). Sakaki et al. (20) reported that MTWA values higher than 65 microvolt were related with cardiac mortality in adult patients with left ventricular dysfunction.

In our study, the MTWA values in all leads were higher in the ES group than in the controls. However, the increase in the MTWA value was only significant in lead V5. In the study conducted by Makarov and Komoliatova (7), which to the best of our knowledge is the only study conducted using the same method as ours in children with congenital heart disease and/or acquired heart disease, maximal values of MTWA were found in lead V5 in 58 patients (86%), in lead V1 in six patients (9%), and in lead aVF in four patients (5%) (7). Similar to this study, using a similar method, we have also acquired the maximum values that reached the highest level significantly in only lead V5. When the Holter ECG recordings of our patients were examined, severe arrhythmia was not observed in any of them. However, there was a history of syncope in three patients who had increased MTWA values. These results suggested to be considered with severe arrhythmia and sudden cardiac death in patient with increased MTWA values. The results of the study conducted by Makarov and Komoliatova (7) revealed that MTWA values were significantly increased in the group with heart disease, which was conducted on 68 children (20 newborns and 48 children aged between 7 and 17 years) and 85 pediatric patients. In another study with spectral-based MTWA method, pathological MTWA values related with high risk were obtained in 304 pediatric patients with cardiac disease. In the same study, it was reported that low MTWA values had a relatively increased negative predictive value and did not exclude the potential of severe sustained ventricular arrhythmia (8).

In our study, it was observed that the left ventricular eccentricity index was significantly decreased in addition to RV hypertrophy and dilatation in the patient group. Since our patients were only those with ES, left ventricular systolic functions were not affected severely as expected. We followed up 13 patients with ES approximately 53 months before the study and did not detect any mortality during this period. It has been well known that MTWA values reflect spatiotemporal heterogeneity during repolarization of the left ventricular myocardium. Generally, the RV mass is smaller than the left ventricular mass and contributes very little toward the formation of T-wave. However, electrical instability has been shown by MTWA because of heterogeneous repolarization of the hypertrophic right ventricle in PAH patients. In patients with PAH, left ventricular functions are also affected in addition to RV functions. While prolonged RV contraction time leads to ventricular asynchronization, flattening of the septum related with increased RV pressure and paradoxal movement toward LV in early diastole disrupt left ventricular filling (21). There seems to be two studies in which the prognostic importance of spectral-based MTWA results have been emphasized in adult PAH patients (22, 23). Lewicka et al. (22) have found that mainly a poorer LV, and only to a lesser degree a poorer RV function, was positively correlated with MTWA result. It has been found that a change in the structure and function of RV also affects LV. However, the prognostic importance of MTWA could not be assessed completely because of limited number of patients; thus, a low mortality rate occurs in this study (22). Another study among PAH patients found a high prevalence of abnormal results of MTWA testing, although left ventricular systolic function is normal (23).

In adult PAH patients, 6-MWD has been shown to be correlated with the parameters that determine the disease severity including WHO-functional class and has been proposed to be a predictor of outcome. Therefore, 6-MWD has been commonly used as an endpoint in treatment efficacy studies (9). Studies and information related with this test in children are limited. In pediatric PAH patients, it has been shown that 6-MWD is an independent determinant in monitoring the prognosis in PAH and can be used as a treatment goal (24). In addition, it has also been reported that significant decrease in tcSO2, especially in the patient group with shunt during 6-MWD, is an additional risk factor in terms of prognosis (24). Our study group had only one patient group with shunt. In the ES group, the mean walking distance was found to be 271.85±77.01 m. When tcSO2 was evaluated before and during 6-MWD, oxygen saturation was observed to be significantly reduced. More importantly, a negative correlation was found between 6-MWD and lead V5 in pediatric ES patients. MTWA values have been shown to increase in patients with decreased exercise tolerance. With this result, it was thought that MTWA may be used as a significant marker of sudden cardiac arrhythmias in survival in pediatric ES patients. Since our study group was a homogeneous ES group, no severe arrhythmia or sudden death was observed because of presence of shunt; thus, the study had a better functional capacity than other studies on causes of PAH in the literature. Although the importance of MTWA values in predicting the development of arrhythmia were shown in other studies, the value of this negative correlation could not be demonstrated clearly because arrhythmia and sudden death did not occur in our study group. Studies with longer follow-up periods investigating the risks of development of sudden death and arrhythmia are required to obtain definite results.

The lack of normal values for MMA for ambulatory MTWA test in children was one limitation of the study. Therefore, a control group was used in our study.

Conclusion

The MTWA lead V5 values were higher in children with ES than in healthy children. These values were also correlated with 6-MWD. Further studies are required to determine the cutoff levels

of MTWA as well as the possible predictive values for arrhythmia or cardiovascular mortality in pediatric patients.

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Peer-review: Externally peer-reviewed.

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