

Eisenmenger syndrome: identifying the clues for arrhythmia

Eisenmenger sendromu: Aritmi geliştirme riskini değerlendirmede kullanılacak ipuçlarını tanımlama

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ABSTRACT

Objective: The aim of this case-controlled, cross-sectional study is to investigate the tendency towards arrhythmia using noninvasive arrhythmia markers (QT dispersion and heart rate variability) in children with Eisenmenger syndrome.

Methods: We studied 23 patients, whose pulmonary-to-systemic resistance ratio was calculated to be greater than 0.75, and who were diagnosed as Eisenmenger syndrome between 1990 and 2001. Twenty healthy children were studied as the control group. Electrocardiographic recordings with calculation of QT dispersion, Holter monitoring, echocardiographic studies and heart rate variability (HRV) analysis were performed in both groups. Catheterization records were analyzed in all the patients.

Results: QT and QTc dispersion were higher ($p=0.007$ and $p=0.006$, respectively) and PR interval was longer ($p=0.009$) in the patients with Eisenmenger syndrome, than those in the control group. In addition, low frequency component, high frequency component, very low frequency component, and total power, obtained from HRV analysis were significantly lower in the patients with Eisenmenger syndrome ($p=0.001$, $p=0.006$, $p=0.009$ and $p=0.011$, respectively). Evaluation of Holter recordings revealed pathologic findings in 21.7% of the patients with Eisenmenger syndrome. Pulmonary-to-systemic resistance ratio of the patients with pathologic Holter findings were higher than in the patients with normal Holter recordings ($p=0.011$). It was also shown that there was a positive correlation between QT dispersion and pulmonary-to-systemic resistance ratio ($p=0.048$, $r=0.416$) and between QT dispersion and PR interval ($p=0.009$, $r=0.532$) in the patients with Eisenmenger syndrome.

Conclusion: Dispersion of repolarization, being associated with high pulmonary-to-systemic resistance ratio, is increased and autonomic modulation of heart rate is impaired in patients with Eisenmenger syndrome. These findings suggest that arrhythmia risk for patients with Eisenmenger syndrome is higher than in normal controls. (*Anadolu Kardiyol Derg 2008; 8: 32-7*)

Key words: Arrhythmia, Eisenmenger syndrome, electrocardiography, QT interval, heart rate variability

ÖZET

Amaç: Bu olgu kontrollü, enine kesit çalışmanın amacı, Eisenmenger sendromlu çocuklardaki aritmiye yatkınlığı, girişimsel olmayan aritmi belirteçleri (QT dispersiyonu ve kalp hızı değişkenliği) kullanarak araştırmaktır.

Yöntemler: Bin dokuz yüz doksan ila 2001 yılları arasında, pulmoner sistemik direnç oranları 0.75'in üzerinde bulunan ve Eisenmenger sendromu tanısı alan 23 hasta çalışmaya dahil edildi. Sağlıklı yirmi çocuk da kontrol grubu olarak alındı. Her iki gruptaki çocukların elektrokardiyografik (QT dispersiyon) ve ekokardiyografik incelemeleri yapıldı, 24 saatlik Holter kayıtları alındı ve kalp hızı değişkenliği analizi değerlendirildi. Kateterizasyon kayıtları Eisenmenger sendromlu grupta gözden geçirildi.

Bulgular: Eisenmenger sendromlu hastalarda kontrol grubuna oranla QT ve QTc dispersiyon değerleri yüksek (sırası ile $p=0.007$ ve $p=0.006$) ve PR intervali uzun ($p=0.009$) bulundu. Bunun yanı sıra kalp hızı değişkenliği parametrelerinden düşük frekans, yüksek frekans, çok düşük frekans ve total güç değerleri, Eisenmenger sendromlu hastalarda anlamlı olarak düşük bulundu (sırası ile $p=0.001$, $p=0.006$, $p=0.009$ ve $p=0.011$). Holter kayıtlarının incelemesi Eisenmenger sendromlu hastaların %21.7'sinde patolojik bulgu olduğunu gösterdi. Patolojik Holter kayıtları olan hastaların pulmoner sistemik direnç oranlarının normal Holter kayıtları olan hastalara oranla daha yüksek olduğu bulundu ($p=0.011$). Ayrıca, Eisenmenger sendromlu hastaların QT dispersiyonları ile pulmoner sistemik direnç oranları arasında ($p=0.048$, $r=0.416$) ve QT dispersiyonları ile PR intervali arasında ($p=0.009$, $r=0.532$) pozitif korelasyonlar olduğu saptandı.

Sonuç: Eisenmenger sendromlu çocuklarda kalp hızının otonomik modülasyonunun bozulduğu ve yüksek pulmoner-sistemik direnç oranı ile de ilişkili bulunan ventriküler repolarizasyonun dispersiyonunun ise artmış olduğu saptanmıştır. Bu bulgular, Eisenmenger sendromlu hastaların, sağlıklı kontrol grubuna oranla daha yüksek oranda aritmi riski taşıdığını düşündürmektedir. (*Anadolu Kardiyol Derg 2008; 8: 32-7*)

Anahtar kelimeler: Aritmi, Eisenmenger sendromu, elektrokardiyografi, QT intervali, kalp hızı değişkenliği

Introduction

Eisenmenger syndrome consists of pulmonary hypertension due to high pulmonary vascular resistance with reversed or bidirectional shunts at the aorticopulmonary, ventricular, or atrial levels (1). The likelihood of developing Eisenmenger syndrome depends on the size and location of the intracardiac defect. Among patients with ventricular septal defects, 3% of the patients who have a small or moderate-sized defect (equal and less than 1.5 cm in diameter) and about half of the patients who have a large defect (more than 1.5 cm in diameter) develop Eisenmenger syndrome (2). Among patients who have a large defect, Eisenmenger syndrome develops in nearly all patients with truncus arteriosus, about half of those with ventricular septal defects or patent arterial ducts, and only in about 10% of those with atrial septal defects (3).

The long-term prognosis of patients with Eisenmenger syndrome is substantially better than that of patients with other conditions associated with pulmonary hypertension (4). Variables associated with a poor long-term outcome are syncope, elevated right heart filling pressure, and severe hypoxemia (systemic oxygen saturation less than 85%) (5, 6). These conditions identify patients with advanced pulmonary vascular disease, severely impaired right ventricular function, decreased cardiac output, or inadequate oxygenation. Most patients with the Eisenmenger syndrome die of sudden cardiac death (5, 7, 8), probably due to a ventricular arrhythmia.

Several electrocardiographic indices, including reduced heart rate variability (HRV) and increased dispersion of repolarization are considered as the noninvasive arrhythmia markers (9-14).

In this study, we aimed to assess the risk factors for the development of arrhythmia using noninvasive arrhythmia markers QT dispersion and heart rate variability in patients with Eisenmenger syndrome in comparison to healthy controls.

Methods

Patients: Twenty-three patients (9 females and 14 males), whose pulmonary-to-systemic resistance ratio was calculated to be greater than 0.75 via hemodynamic data, obtained during cardiac catheterization, and who were diagnosed with Eisenmenger syndrome (study group) between January 1990 and December 2001 at Hacettepe Children's Hospital, Department of Pediatric Cardiology were included in this cross-sectional case-controlled study. Twenty healthy children were also studied as the control group. The study exclusion criteria were: Known risk factors causing prolongation of QT interval, such as certain drugs, dietary deficiencies, metabolic disturbances, possible other familial diseases and long QT syndrome.

The informed consent of patients and their parents were obtained.

Clinical and hemodynamic records: Ages at the time of diagnosis of congenital heart disease and Eisenmenger syndrome were obtained from the medical records of the patients. New York Heart Association (NYHA) functional classification system was used for the clinical evaluation of the patients. Cardiac catheterization and angiography records of the patients with Eisenmenger syndrome were reviewed. Pulmonary

flow (Qp) and systemic flow (Qs) were calculated by the use of the Fick formula. Pulmonary vascular resistance (Rp) and systemic vascular resistance (Rs) were calculated using the following formulas: $R_p = \text{mean pulmonary artery pressure} - \text{mean left atrium pressure} / Q_p$, $R_s = \text{mean aortic pressure} - \text{mean right atrium pressure} / Q_s$. In addition, left-to-right shunt, right-to-left shunt, left atrial pressure, right atrial pressure, mean pulmonary arterial pressure, and mean aortic pressure recordings were also evaluated.

Electrocardiography: Twelve-lead electrocardiogram was recorded with a three-channel electrocardiographic recorder at a paper speed of 25 millimeters per second. Two different observers evaluated all the electrocardiograms. The QT intervals were measured from the first deflection of the QRS complex to the point of T wave offset, defined by return of terminal T wave to the isoelectric T-P interval baseline. In the presence of a U wave interrupting the T wave, the terminal portion of the visible T wave was extrapolated to the T-P interval baseline to define the point of T-wave offset. Three consecutive cycles in each of the 12 leads were measured and mean QT interval was calculated. At least nine leads in which the QT interval could be measured were required for QT dispersion calculation. QT dispersion was defined as the difference between the minimal and maximal QT intervals. Each QT interval was corrected by heart rate according to Bazett's formula [$QT_c = QT / (R-R)^{1/2}$] and then QTc dispersion was calculated.

Echocardiography: Echocardiograms were performed for both groups with 2-D guided M-mode echocardiography with transducer frequencies appropriate for body size. M measurements were performed according to the American Society of Echocardiography recommendations (15).

Holter monitoring and HRV analysis: Heart rate variability was determined for both groups from 24-hour Holter recording using a Holter for Windows-Rozinn 800/648-8840 system (Rozinn Electronics Inc, Glendale, NY, USA). The following measures of HRV were calculated: standard deviation of RR intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (NN50), percentage of successive pairs of NN intervals differing by > 50 ms (PNN50), the energy in power spectrum between 0.003 and 0.04 Hz (VLF, very low frequency power), the energy in power spectrum between 0.04 and 0.15 Hz (LF, low frequency power), and the energy in power spectrum between 0.15 and 0.40 Hz (HF, high frequency power). Holter recordings were evaluated with respect to ventricular arrhythmias according to Lown criteria.

Statistical analyses

The SPSS 11.0 statistical package for Windows (Chicago, IL, USA) was used. The means and standard deviations of normally distributed variables, and medians (median, minimum-maximum) of variables not normally distributed were calculated. Nominal values were presented as percentage. Numeric independent normally distributed values were evaluated by Student's unpaired t-test, values not normally distributed - by Mann Whitney U test, and nominal values by Chi-square, or Fisher's Chi-square test. A p value below than 0.05 was considered significant.

Results

The characteristics of the study groups are shown in Table 1. The patients and control groups did not differ by means of age, sex, body weight and height.

Characteristics of Eisenmenger syndrome patients are given in Table 2. Mean oxygen saturation of the patients with Eisenmenger syndrome were found to be $87.5 \pm 8.3\%$. Patients were diagnosed as congenital heart disease at the median age of 0.5 (0.08-13 years) years, and received the diagnosis of Eisenmenger syndrome at the median age of 7.00 (0.6-22) years. Mean pulmonary-to-systemic resistance ratio and pulmonary flow over systemic flow ratios of the patients with Eisenmenger syndrome were found to be 1.12 ± 0.72 and 1.07 ± 0.29 , respectively. The ratio of left-to-right to right-to-left shunt was found to be approximately 1. Mean pulmonary flow and mean pulmonary vascular resistance of the patients were 4.32 ± 1.75 L/min/m² and 21.02 ± 16.84 Um², respectively, and mean pulmonary arterial pressure and mean aortic pressure were found to be 74.7 ± 12.1 mmHg and 72.2 ± 12.9 mmHg, respectively.

Echocardiographic examination of both groups showed that 19 patients with Eisenmenger syndrome (82%) had ventricular septal defect, 7 patients (30.4%) - atrial septal defect, 5 patients (22.7%) - patent arterial duct, 12 patients (54.5%) - mitral regurgitation, 2 patients (9.1%) - aortic regurgitation, 17 patients (77.3%) - pulmonary regurgitation, 16 patients (72.7%) - tricuspid regurgitation, and 1 patient (4.3%) - coarctation of the aorta. When right and left ventricular functions of the two groups were compared, no statistically significant difference was found, except for smaller diastolic diameter of interventricular septum (0.526 ± 0.180 cm vs 0.629 ± 0.109 cm) and larger diameter of the left atrium (27.7 ± 7.4 mm vs 21.6 ± 4.7 mm) in the patients with Eisenmenger syndrome as compared with healthy controls ($p=0.036$, and $p=0.003$, respectively) (Table 3).

Electrocardiograms of the patients with Eisenmenger syndrome showed that PR intervals were longer than that of the healthy controls (0.138 ± 0.025 s vs. 0.120 ± 0.017 s, $p=0.009$). The mean QT dispersion (58.2 ± 21.6 ms vs. 42.0 ± 14.3 ms, $p=0.007$) and QTc dispersion (73.0 ± 28.4 ms vs. 52.3 ± 16.6 ms, $p=0.006$) values were higher in patients with Eisenmenger syndrome than in healthy controls.

There was no significant difference between the two groups in terms of the findings of Holter monitoring ($p=0.051$). Five patients with Eisenmenger syndrome (patients with number 3, 6, 15, 19, and 21) had pathologic Holter findings. One of them had first-degree atrioventricular block with uniform, rare premature ventricular contractions; one had rare, uniform premature ventricular contractions; one had rare, premature atrial contractions; one had frequent premature ventricular

contractions with couplets; and one had premature atrial contractions with short episodes of supraventricular tachycardia.

The HRV records differed between the groups only in values of VLF, LF, HF components, and total power (Table 4). All these values were found to be lower in patients with Eisenmenger syndrome as compared with healthy controls ($p=0.009$, $p=0.001$, $p=0.006$, and $p=0.011$, respectively).

In order to investigate the tendency towards arrhythmias, we evaluated the relationship of QT dispersion and HRV with echocardiographic and catheter angiographic data of the patients with Eisenmenger syndrome. There was a positive correlation between QT dispersion and pulmonary-to-systemic resistance ratios ($p=0.048$, $r=0.416$). Moreover, a positive correlation was also found between QT dispersion and PR interval ($p=0.009$, $r=0.532$) and between PR interval and right atrial pressure values ($p=0.015$, $r=0.500$). A significant inverse correlation was found between HF component and tricuspid regurgitation velocity of 16 patients with Eisenmenger syndrome ($p=0.016$, $r=-0.849$).

Comparison of electrocardiographic (PR interval, QT dispersion, QTc dispersion) and hemodynamic (pulmonary arterial pressure, pulmonary vascular resistance and pulmonary-to-systemic resistance ratio) in patients with normal and pathologic Holter monitoring findings showed that only pulmonary-to-systemic resistance ratio was significantly higher in patients with pathological Holter findings (1.73 ± 1.34 vs. 0.96 ± 0.35 , $p=0.011$).

Discussion

Our study demonstrated increased spatial dispersion of repolarization and reduced heart rate variability in unselected patients with Eisenmenger syndrome. The increased dispersion of repolarization was positively correlated with hemodynamic index – pulmonary-to-systemic resistance ratio and the latter one was found to be higher in patients with positive findings on Holter monitoring. The high frequency component of HRV was inversely related with the severity of tricuspid regurgitation.

Arrhythmias are major causes of morbidity and mortality in patients with Eisenmenger syndrome. The major arrhythmias are atrial fibrillation and flutter. They are particularly associated with atrial septal defects and with severe atrioventricular valve regurgitation. It would be reasonable to suspect that sudden deaths in the Eisenmenger population could be arrhythmic in origin. Arrhythmia (supraventricular or ventricular) may operate on its own or may produce acute worsening of cardiac performance and output, leading to death. When examining the risk factors for death in patients with Eisenmenger syndrome, it would therefore be reasonable to focus attention on factors

Table 1. Characteristics of the study population

	Age, years	Sex, Male/Female	Body weight, kg	Height, cm
Patients with Eisenmenger syndrome (n=23)	11.21 ± 5.04	9/14	29.95 ± 15.88	131.5 ± 30.6
Healthy controls (n=23)	10.35 ± 4.81	8/12	35.27 ± 16.54	135.6 ± 27.7
p *	0.634	0.954	0.214	0.715
Data are expressed as Mean±SD and numeric values * - "p" values for Student's t-test and Chi-square test				

associated with heart failure and to attempt to separate them from those, which may predispose to sudden arrhythmic death. This may in turn provide a clinical management algorithm that is individually tailored. Therefore, evaluation of arrhythmias in patients with Eisenmenger syndrome is of crucial importance. The evaluation of arrhythmia always begins with a careful history and physical examination, but generally requires more sophisticated and comprehensive noninvasive and invasive investigation. Electrocardiogram, QT and QTc dispersion, PR interval, heart rate variability, and 24-hour Holter monitoring are the noninvasive techniques for evaluating the tendency to arrhythmias in patients with Eisenmenger syndrome.

In the present study, no arrhythmia was found to be present on electrocardiograms. However, PR intervals measured on electrocardiograms were found to be longer in Eisenmenger patients than in the controls. It is known that prolongation of PR interval is associated with the risk of atrial fibrillation (9). This was also supported by the finding of positive correlation between PR interval and right atrial pressure of patients with Eisenmenger syndrome in the present study. Increase in right atrial pressure caused an increase in PR interval, and this may be associated with the risk of atrial fibrillation. Additionally, QT and QTc dispersion of the patients were found to be higher than in the controls. It has been proposed as a non-invasive electrocardiographic parameter that might predict an increased

Table 2. Characteristics of patients with Eisenmenger syndrome

Case number	Sex	Age, years	Body weight, kg	Length, cm	Diagnoses*	Age at the time of diagnosis of congenital heart disease (**)	Age at the time of Eisenmenger syndrome (**)	NYHA classification	O ₂ saturation, %
1	F	17	44	157	PDA, ES	3-year-old	5.5-year-old	1	75.6
2	M	9	22	112	Complete atrioventricular septal defect, common atrioventricular valve regurgitation, mitral cleft, ES, Down syndrome	1-month-old	4-year-old	2	91
3	F	14	29	145	Situs inversus totalis, malposition of great vessels, VSD, ES	2-year-old	13-year-old	3	85
4	M	6	17	108	VSD, ASD, ES	5-month-old	3-year-old	1	93.4
5	F	8	17	107	Large inlet VSD, ES, Down syndrome	3-month-old	4-year-old	2	92
6	M	16	63	185	VSD, PH, ES, operated PDA	5-month-old	11-year-old	1	80
7	F	8	17.5	117	VSD, PDA, ES	2-year-old	3-year-old	1	96
8	F	9	29.5	136	ASD, PH, ES	1.5-year-old	3-year-old	2	91.1
9	F	9	16.5	112	Double outlet right ventricle, VSD, ES	1-year-old	8-year-old	1	97
10	M	17	46	163	VSD, ES	13-year-old	15-year-old	1	93
11	F	6	11.5	93	VSD, PH, ES	6-year-old	6-year-old	1	92.4
12	M	6	12	85	VSD, PH, ES	7-month-old	1.5-year-old	1	86.7
13	F	9	29	120	Complete atrioventricular septal defect, common atrioventricular valve regurgitation, PDA, ES	5-month-old	3-year-old	1	92
14	M	17	45	172	CTGA, VSD, coronary abnormality, ES	3-month-old	8-year-old	1	82
15	F	22	50	150	Coarctation of aorta, PDA, aorticopulmonary window, ES	3-month-old	22-year-old	3	89
16	F	15	42.5	152	VSD, PH, ES	8-year-old	15-year-old	2	91.4
17	F	10	28	137	VSD, PH, ES	6-month-old	2-year-old	1	82
18	F	1	5.5	66	Complete atrioventricular septal defect, common atrioventricular valve regurgitation, ES, Down syndrome	1-month-old	7-month-old	3	67
19	M	17	51	165	VSD, PH, ES	1-year-old	7-year-old	2	90
20	F	7	18	110	Complete atrioventricular septal defect, common atrioventricular valve regurgitation, ES	6-month-old	7-year-old	2	95.6
21	M	15	52	171	Malposition of great vessels, univentricle, ES	6-month-old	15-year-old	1	92
22	F	9	20	125	Large VSD, PH, ES	1-month-old	9-year-old	2	89.9
23	F	11	23	138	Large VSD, large ASD, mitral stenosis, ES	2-month-old	8-year-old	1	68

* valve regurgitations are not shown in this column

**age is expressed in months for patients below one year of age, and in years for older patients

ASD- atrial septal defect, CTGA- corrected transposition of great arteries, ES- Eisenmenger syndrome, PDA- patent arterial duct, PH- pulmonary hypertension, VSD- ventricular septal defect

risk of malignant arrhythmias (10). The normal range for QT dispersion is 40-50 ms, with a maximum of 65 ms (11). The risk for serious ventricular arrhythmias or sudden death has been observed in subjects with QT dispersion greater than 65 ms. The prolongation in QT and QTc dispersion observed in the present study may indicate an increased risk of cardiac arrhythmias. In the present study, increased QT dispersion positively correlated with pulmonary-to-systemic resistance ratio in patients with Eisenmenger syndrome. This might indicate an increased risk of ventricular arrhythmias in a patient with high pulmonary-to-systemic resistance ratio. A positive correlation found between QT dispersion and PR interval in patients with Eisenmenger syndrome support the idea that these parameters might be used in the evaluation of arrhythmias in Eisenmenger syndrome.

Holter recordings showed pathological findings in 21.7% of the patients with Eisenmenger syndrome. Comparison of pulmonary-to-systemic resistance ratios of the patients with normal and pathological findings showed a higher pulmonary-to-systemic resistance ratio in patients with pathological Holter recordings. In the present study, this finding also might be accepted as another clue showing the relationship between increased arrhythmia risk and high pulmonary vascular resistance.

Heart rate variability determined in the time and frequency domain can be used to assess the cardiac autonomic status noninvasively. Previous studies suggest marked reduction of HRV in patients with heart failure (12-14). Experimental and clinical studies have reported that both increased sympathetic and decreased parasympathetic tone may interact with the electrophysiological mechanisms underlying arrhythmogenesis.

Table 3. Echocardiographic data of the patients with Eisenmenger syndrome and healthy controls

Parameters	Patients with Eisenmenger syndrome (n=23)	Healthy controls (n=23)	p*
IVSD, cm	0.526 ± 0.180	0.629 ± 0.109	0.036
LVDD, cm	3.94 ± 1.04	4.08 ± 0.73	0.618
LV PWD, cm	0.644 ± 0.200	0.574 ± 0.153	0.223
IVSS, cm	0.764 ± 0.288	0.806 ± 0.179	0.590
LVDS, cm	2.33 ± 0.64	2.51 ± 0.53	0.323
LVPWS, cm	0.840 ± 0.247	0.931 ± 0.249	0.257
LVEF, %	0.702 ± 0.087	0.700 ± 0.043	0.946
LVSF, %	0.394 ± 0.070	0.388 ± 0.034	0.714
RVDD, cm	3.60 ± 1.15	3.08 ± 0.38	0.129
RVDS, cm	2.55 ± 0.92	2.19 ± 0.27	0.180
RVEF, %	0.622 ± 0.071	0.598 ± 0.049	0.275
RVSF, %	0.328 ± 0.054	0.305 ± 0.339	0.164
Ao diameter, mm	19.3 ± 5.0	19.5 ± 4.1	0.890
LA diameter, mm	27.7 ± 7.4	21.6 ± 4.7	0.003

Data are represented as Mean ± standard deviation; *- Student's unpaired t-test
Ao- aorta, IVSD- interventricular septum diastolic diameter, IVSS- interventricular septum systolic diameter, LA- left atrium, LVDD- left ventricle diastolic diameter, LVDS- left ventricle systolic diameter, LVEF- left ventricular ejection time, LVPWD- left ventricle posterior wall diastolic diameter, LVPWS- left ventricle posterior wall systolic diameter, LVSF- fractional shortening of left ventricle, RVDD- right ventricle diastolic diameter, RVDS- right ventricle systolic diameter, RVEF- right ventricular ejection time, RVSF- fractional shortening of right ventricle

Reduced heart rate variability was interpreted as a result of predominantly sympathetic and reduced vagal modulation of sinus node (14). Major marker for vagal activity is accepted as the HF component. Low frequency component is accepted as marker for sympathetic activity, but also in some studies, accepted as a marker for both sympathetic and parasympathetic activity. One can speculate that, development of arrhythmias is associated with a decreased vagal activity and increased sympathetic activity, which are reflected by HF component and LF component respectively. In the present study all spectral components of HRV were found to be lower in patients with Eisenmenger syndrome as compared with controls. Decreased HF component, VLF component and total power might indicate an increased risk of arrhythmias. In the present study, reduction in LF component was an unexpected finding. This finding may be explained as a change in the responsiveness of pacemaker cells to neural inputs as a result of a persistent neurohumoral sympathetic activation that is not opposed, by vagal activity (14). We also observed a negative correlation between tricuspid regurgitation velocity and HF component of HRV of the patients with tricuspid regurgitations. One can speculate that this might indicate an increased risk of arrhythmias in a patient with high tricuspid regurgitation velocity.

Limitations of the study

This study was the case-controlled, cross-sectional study and was not designed to examine the prospective follow-up of the patients with Eisenmenger syndrome. Therefore, no information about the progression of the disease and development of arrhythmia is available. The small sample size is also a limitation of our study. Further studies with larger sample sizes and longer follow-up periods could provide additional information.

Conclusion

Present study not only confirmed the well-known relation between arrhythmias and Eisenmenger syndrome, but, in addition, showed that the patients with Eisenmenger syndrome

Table 4. Heart rate variability findings of the patients with Eisenmenger syndrome and healthy controls

Parameters	Patients with Eisenmenger syndrome (n=23)	Healthy controls (n=20)	p
SDNN, ms*	129.8 ± 45.8	140.9 ± 61.8	0.947
RMSSD, ms*	62.65 ± 44.7	74.0 ± 31.5	0.188
NN50 *	16302 ± 12686	16094 ± 8935	0.808
PNN50, %*	19.2 ± 13.9	25.9 ± 15.9	0.238
Log VLF**	2.1 (3.2, 1-8.3)	4.7 (6.2, 1.5-20)	0.009
Log LF**	1.3 (1.48, 1-3.1)	1.8 (4.89, 1.2-53)	0.001
Log HF**	1.2 (1.47, 1-4.6)	1.45 (1.78, 1.1-6.6)	0.006
Log total power**	3.9 (14.8, 1.1-120)	9.7 (343.3, 2-5800)	0.011

* - Mean ± standard deviation - Student's unpaired t-test

** - Median (Mean, Minimum-Maximum) - Mann Whitney U test

HF- the energy in power spectrum between 0.15 and 0.40 Hz (high frequency power), LF- the energy in power spectrum between 0.04 and 0.15 Hz (low frequency power), NN50- number of pair of adjacent NN intervals differing by more than 50 ms in the entire recording, PNN50- percentage of successive pairs of NN intervals differing by > 50 ms, RMSSD- the square root of the mean of the sum of the squares of differences between adjacent NN intervals, SDNN- standard deviation of RR intervals, VLF- the energy in power spectrum between 0.003 and 0.04 Hz (very low frequency power)

have increased spatial dispersion of repolarization, and reduced spectral indices of heart rate variability, which were correlated with the clinical and hemodynamic indices. The value of these abnormalities in the prediction of arrhythmia and sudden death in patients with Eisenmenger syndrome should be validated in further prospective studies.

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