High-Resolution Electrocardiography in Patients with Eisenmenger Syndrome

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Abstract

Eisenmenger syndrome (ES) represents the severest end of the disease spectrum of pulmonary arterial hypertension associated with congenital heart disease. Structural and electrical remodeling of the right ventricle is characteristic of ES. We aimed to evaluate advanced ECG parameters using high-resolution electrocardiography (HR-ECG) in ES patients.

Twenty adult ES patients (75% female, mean age 39.6±12 years) without arrhythmias, permanent ventricular pacing, acute or advanced heart failure were included and compared to 40 controls of the same age and sex. Each participant underwent a 5-minute HR-ECG recording at rest. Several parameters were analyzed using dedicated software. Significant abnormalities in several HR-ECG parameters of heart rate variability, ventricular depolarization and repolarization, ventricular gradient, and HR-ECG scores were observed in ES patients compared to healthy controls.

Results of our HR-ECG study show altered cardiac autonomic function, ventricular depolarization, and repolarization in patients with ES. The prognostic value of these simple and easily acquired parameters warrants further investigation in more extensive studies.

1. Introduction

Patients with Eisenmenger syndrome (ES) represent the severest end of the disease spectrum of patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD). In contrast to other PAH groups, right ventricular (RV) pressure overload in ES is present from an early age, and systemic output is maintained by increasing right-to-left shunt at the expense of central cyanosis. Survival of ES patients is better compared to other PAH patients. However, life expectancy remains markedly reduced despite advances in medical therapy [1,2].

Arrhythmias are common long-term complications, and sudden cardiac death is the most common cause of death in ES patients [1,3]. Chronic pressure overload due to PAH leads to structural, functional, and electrical remodeling of the right ventricle, providing a potential arrhythmogenic substrate.

These changes can be non-invasively assessed using electrocardiography (ECG). Standard ECG parameters such as QRS and corrected QT (QTc) duration are known prognostic markers in ES patients [1,4,5]. Conversely, studies using advanced and novel ECG markers are scarce. In non-CHD patients, advanced markers of cardiac autonomic function, ventricular depolarization, and repolarization were shown to be valuable clinical risk markers for arrhythmias and SCD [6].

The aim of our study was to evaluate advanced high-resolution electrocardiography (HR-ECG) parameters in adult ES patients. Furthermore, we wanted to assess the possible relationships of these parameters to other established prognostic clinical, laboratory, and imaging markers.

2. Methods

This single-center observational study included consecutive adult patients with ES that presented to our outpatient department. Patients with chronic atrial fibrillation or other uncontrolled arrhythmias, permanent ventricular pacing, acute or advanced chronic heart failure (NYHA 4) were excluded. A control group of healthy adults of the same age and sex was selected from a previously reported large group of apparently healthy individuals [7].

Each participant had a resting 5-minute-long high-resolution ECG recording acquired using a 1000-Hz dedicated recording device (Cardiax, IMED, Budapest, Hungary) with no filter applied. All recordings were performed in a quiet room without electronic interferences to minimize the artifacts and with the patient in the supine position, breathing normally. Author developed (VS) software was used to analyze several classic and advanced ECG parameters. The study was performed following the Declaration of Helsinki and approved by Slovenian Medical Ethics Committee.

2.1. Cardiac autonomic function parameters

Cardiac autonomic function was assessed by heart rate variability (HRV). Time-domain parameters included standard deviation (SD) of all normal RR (NN) intervals (SDNN) which is a global index of HRV, and the square root of the mean of the sum of squares of successive NN interval differences (rMSSD), which reflects short-term parasympathetic nervous system (PSN) changes. Frequency domain parameters were obtained using Lomb periodogram or autoregressive model and included total power (LoTo), power in the high-frequency range (0.15–0.4 Hz) representing PSN changes (LoHF), and in the low-frequency range (0.04–0.15 Hz) representing overall autonomic nervous system activity (LoLF).

2.2. Ventricular depolarization and repolarization parameters

Ventricular depolarization parameters included presence of right bundle branch block (RBBB) pattern, QRS duration (QRSd), high-frequency QRS complex mean peak amplitude (HFQRS_A) determined by singular value decomposition, and QRS slope represented by maximal QRS downstroke (dVdt2).

The following parameters evaluated ventricular repolarization: the QTc interval duration, the standard deviation of the normal-to-normal QT interval (SDNN_QT), QT variability index obtained using means and variances of the beat-to-beat QT and RR interval (QTVi) [7], angle between QRS and T complex derived from 3-dimensional ECG (QRS-T angle) [8], the intradipolar ratio of T wave expressed as natural logarithm (Ln_IDRT), and T wave residuum (TWR) that were obtained via singular value decomposition [9].

2.3. Ventricular gradient and multi-parameter ECG scores

Spatial ventricular gradient in the x-axis (VG-x) and the recently developed direction optimized spatial ventricular gradient for RV pressure overload (VG-RVPO) were calculated [10].

RV strain was assessed by a previously described score (RV-score) that combines several established ECG parameters [11]. Furthermore, validated multi-parameter advanced ECG scores for "Disease" in general and for left ventricular systolic dysfunction (LVSD5) were also studied [9, 11].

2.4. Clinical and imaging data

Clinical data obtained for each patient included history of clinically important arrhythmias, use of PAH-specific medications, N-terminal pro B-type natriuretic peptide (NT-proBNP) level, and 6-minute walking test distance (6MWT). Tricuspid annular plane systolic excursion (TAPSE) was used as an echocardiographic parameter of RV function.

2.5. Statistics

Categorical variables are represented as frequencies and percentages, while continuous variables are presented as mean ± standard deviation (SD). Following testing for normality of distribution (by the Kolmogorov-Smirnov test) all intergroup comparisons were calculated by Mann-Whitney U test. The correlation was determined by Pearson's correlation test. A two-sided p value of 0.05 was considered statistically significant. Statistical analysis was performed in IBM SPSS version 22.0 (IBMCorp., Armonk, N.Y., USA).

Table 1. Comparison of HR-ECG obtained heart rate variability parameters, ventricular depolarization and repolarization, ventricular gradient and multiparameter ECG scores between ES patients and healthy controls.

	ES (n=20)	Controls (n=40)	p
Number of beats	259	255	NS
RR interval (ms)	854	880	NS
HRV			
SDNN	37.4	47.8	**0.002**
rMSSD	52.0	38.2	NS
LoTo	5.74	6.58	**0.010**
LoLF	4.50	5.52	**0.009**
LoHF	4.20	5.20	**0.007**
Depolarization			
RBBB	4 (20%)	0	**0.010**
QRS duration (ms)	127	105	**<0.001**
HFQRS_A (units)	5.1	3.8	**0.020**
dVdt2 (1/ms)	48.3	57.4	**0.020**
Repolarization			
QTc (ms)	417	398	**0.036**
SDNN_QT (ms)	3.2	2.5	NS
QTVi (units)	-1.19	-1.80	**<0.001**
QRS-T angle (°)	109	43	**<0.001**
Ln_IDRT (units)	0.72	-0.28	**<0.001**
TWR (units)	0.39	0.11	**<0.001**
VG			
VG-x	6.8	46.2	**<0.001**
VG-RVPO (mVms)	-2.9	-29.7	**<0.001**
ECG Scores			
RV-score (units)	4.85	1.3	**<0.001**
Disease (units)	3.99	-3.08	**<0.001**
LVSD5 (units)	3.65	4.3	NS

3. Results

Twenty patients (75% female, mean age 39.6±12 years) and forty controls of the same age and sex were included. Most ES patients had a post-tricuspid shunt, only one had an isolated pre-tricuspid shunt (atrial septal defect). Down syndrome was present in ten ES patients (50%). Four ES patients had a history of clinically significant arrhythmias - two had atrial tachyarrhythmia necessitating medical therapy, and two non-sustained ventricular tachycardia. At least one PAH-specific drug was used in 16 ES patients (80%).

Significant abnormalities in several HR-ECG acquired parameters were observed in ES patients compared to healthy controls (Table 1). The best performers were parameters of ventricular repolarization and VG parameters and multi parameter ECG scores (with $p<0.001$) [Table 1].

3.1. Comparison with clinical and imaging data

Comparison in the patient group showed that women had lower VG-RVPO and QTVi, while older patients had higher NT-proBNP levels, longer QRS duration and lower frequency domain HRV parameters. Patients with Down syndrome had higher QRS_T angle, TWR, and RV-score than other ES patients. Patients with a history of clinically significant arrhythmias had higher QT variability index (-0.7 vs. -1.3, p=0.039), and lower HRV parameters in the time and frequency domain (SDNN p=0.002, RMSSD p=0.003; LoTo p=<0.001, LoLF p=<0.001, LoHF p=0.003). Lower LoLF (r=-0.471, p=0.042) and LoHF (r=-0.456, p=0.050) were also associated with higher levels of NT-proBNP. However, no significant correlation was found between these or other HR-ECG parameters and 6-minute walking test distance, PAH specific therapy or TAPSE.

4. Discussion

Our HR-ECG study demonstrated significant abnormalities of cardiac autonomic function, ventricular depolarization and repolarization in adult patients with ES compared to healthy controls.

Cardiac autonomic dysfunction characterized by sympathetic autonomic over activation is associated with heart failure, arrhythmias, and SCD in non-CHD patients. Less is known about the precise role of the autonomic nervous system in patients with predominant RV pathology. We have shown profound changes in both time and frequency domain HRV parameters in adults with ES. Previous reports have shown abnormal time-domain HRV parameters in adult and abnormal frequency-domain HRV parameters in pediatric ES patients [12,13]. These two studies failed to demonstrate any association of HRV and different clinical parameters, while in our patients HRV parameters were more abnormal in ES patients with higher NT-proBNP and a history of clinically significant arrhythmias. Elevated levels of norepinephrine and selective down-regulation of beta-adrenergic receptors can at least partly explain cardiac autonomic dysfunction demonstrated in ES and PAH patients [14]. A large registry study of ES patients has previously shown a trend between beta-blocker therapy and better survival [1], possibly through modulation of cardiac autonomic function, but further studies are needed.

Classical ventricular depolarization and repolarization parameters, such as QRS and QTc duration, are known predictors of prognosis in ES patients [1,4,5]. Our study is the first to show abnormalities in novel and advanced parameters of ventricular depolarization and repolarization in ES patients. These changes are supported by PAH animal studies that showed changes in expression and function of cardiomyocyte ion channels, prolongation and increased dispersion in action potential, and increase in repolarization heterogeneity [15]. Moreover, chronic pressure overload associated with PAH induces RV hypertrophy, which may lead to myocardial ischemia and the development of focal or diffuse myocardial fibrosis [16]. Myocardial fibrosis represents the essential arrhythmogenic substrate, leading to increased vulnerability, arrhythmias, and SCD.

Assessing the correlation between ventricular depolarization and repolarization parameters with clinical markers, only higher QTVi was found to be associated with arrhythmias. QTVi is a known marker of ventricular repolarization heterogeneity associated with ventricular arrhythmias and SCD in non-CHD patients [17]. Changes in QTVi probably reflect the above described structural and electrical RV remodeling in ES patients. A previous study in pediatric ES patients has shown abnormal microvolt T-wave alternans, which is also a marker of ventricular repolarization heterogeneity [18].

Ventricular gradient parameters (VG-x and VG-RVPO) represent ventricular action potential duration heterogeneity and were previously shown to be markers of pulmonary hypertension and RV hypertrophy [10,19]. Thus, markedly abnormal VG-x and VG-RVPO in our patients are not surprising, since ES patients are characterized by severe PAH and RV hypertrophy. Observed values of VG-x correspond well to patients with severe idiopathic PAH [19]. Similarly, both RV and "Disease" ECG scores were also markedly different in ES patients compared to controls.

The study's main limitation was its relatively small number of patients; thus, statistical results should be interpreted with caution. ES is a rare disease; therefore, only multicenter studies can provide larger scale patient populations. Included patients were also clinically heterogeneous (simple and complex ES patients, a large

proportion of Down syndrome patients), leading to potential bias. Four ES patients also had RBBB that might alone be responsible for some differences in ventricular depolarization and repolarization parameters. Although our study provided valuable HR-ECG evidence of a potential arrhythmogenic substrate in ES patients, the limited number of included patients with arrhythmias precluded additional statistical analysis. Therefore, larger studies with more patients are needed to further explore the clinical and prognostic value of the presented HR-ECG parameters.

5. Conclusions

In conclusion, the results of our HR-ECG study show altered cardiac autonomic function, ventricular depolarization and repolarization in adult patients with ES. The clinical and prognostic value of these simple and easily acquired parameters warrants further investigation in more extensive studies.

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