Original paper

Heart rate variability in adult patients with congenital heart disease

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Abstract

Introduction: Heart rate variability (HRV) illustrates an autonomic nervous system influence on the sinus node. It is known that low HRV parameters indicate poor prognosis in patients with myocardial infarction, predict sudden cardiac death and death due to heart failure. Adult population with congenital heart disease (CongHD) is particularly exposed to these complications. The aim of this study was to evaluate HRV parameters in adult patients with CongHD and to analyse the impact of the specific type of CongHD and past cardiac surgery on HRV.
Materials and methods: Data of 345 adult patients aged 18-67 with CongHD were analysed. From the 24-hour ECG monitoring time domain indexes of HRV were calculated: SDNN, SDANN-i, SDNN-I, r-MSSD, pNN50.
Results: All analysed HRV parameters were not different in CongHD patients comparing to the control group, and gradual, physiologic decrease due to aging was also present. Age at operation had no effect on HRV values, except in patients after correction of coarctation of the aorta (SDNNi r=-0.312; p=0.005; rMSSD r=-0.354; p=0.001; pNN50 r=-0.41; p=0.0001) and ventricular septal defect (rMSSD r=-0.310; p=0.02; pNN50 r=-0.336; p=0.01), where a negative correlation was found.
Conclusions: 1. Despite slight differences between subgroups of CongHD patients, HRV values in adult patients with CongHD are similar to those in the healthy population, and gradual, physiologic decrease due to aging is also present. 2. Age at operation does not influence the HRV profile in the general population of patients with CongHD. Age at operation influences HRV in patients with left ventricle overload. Similar relations are not observed in the group with impaired right ventricle hemodynamics.

Key words: heart rate variability, congenital heart disease in adults.

Introduction

Heart rate variability (HRV) illustrates an autonomic nervous system influence on sinus node cell receptors. It has been well known since 1987 that low HRV parameters indicate poor prognosis in patients with myocardial infarction [1-4]. Low HRV parameters were shown to predict sudden cardiac death and death due to hart failure [3-7, 13]. Suppressed HRV is also observed due to hypertension and left ventricle hypertrophy [8, 9, 13-15]. In all these conditions, sympathetic modulation of the sinus node function is elevated in contrary to the parasympathetic one [5, 8 ,11]. Serum

concentration of catecholamines, vasopressin and renin is raised, but the baroreceptors reflex is decreased [9, 16]. Adult population with congenital heart disease (CongHD) is a very diverse group of patients, particularly exposed to the cardiovascular complications mentioned above [17]. There only a few papers on HRV in CongHD, mainly conducted in children [16, 18-26].

The aim of this study was to evaluate HRV parameters in adult patients with CongHD and to analyse the impact of the specific type of CongHD and past cardiac surgery on HRV.

Material and methods

Data of 345 adult patients (171 women) aged 18-67 (mean 31.4±10.8) with CongHD were selected from a database of Adult Congenital Heart Disease Outpatient Clinic of I Cardiology Department in Poznan. The studied patients were free of heart failure, respiratory system disease and diabetes. There was no need for pacemaker implantation nor antiarrhythmic therapy (including beta-blockers) at the time of the study. The sinus rhythm was preserved in all selected patients. The target group consisted of 40 patients (pts) with patent atrial septal defect type II (ASD), 36 pts after ASD II surgical closure (after ASD II), 78 pts with corrected coarctation of the aorta (post CoAo), 20 pts with uncorrected Ebstein' anomaly (Ebstein), 28 pts after patent ductus arteriosus surgical closure (after PDA), 71 after total correction of tertralogy of Fallot (after ToF), 16 pts with patent ventricular septal defect (VSD), 56 pts after VSD surgical closure (after VSD). Most of the above pts (269; aged 18-60; mean 28.84±8.89) had undergone a cardiosurgical procedure, the non-operated (76) pts were aged 20-67 (mean 40.6±11.9). The control group gathered 47 healthy volunteers (22 women) aged 18-64 (mean 33.2±11.3). For the ASD II group we matched another, "older" control group: 29 healthy individuals aged 43.1±6.7 years (14 women). From the 24-hour ECG monitoring

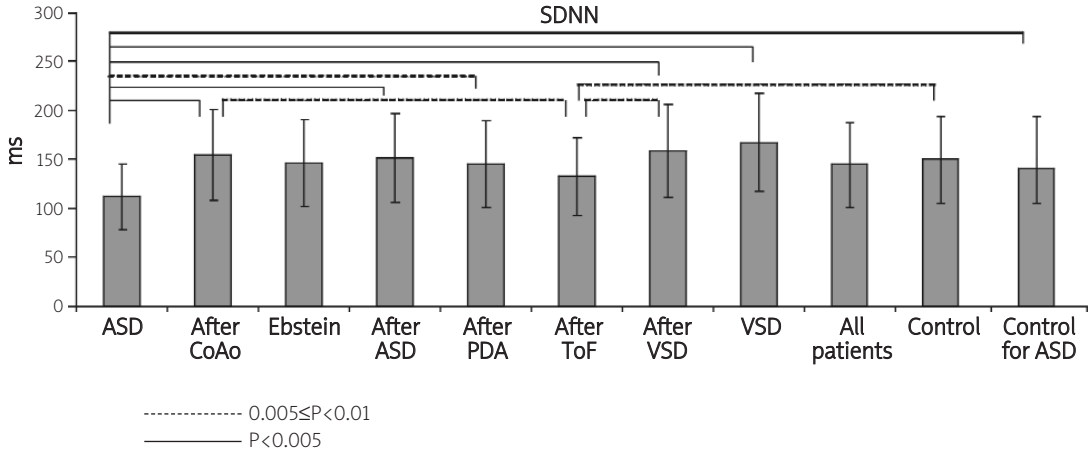

Figure 1. Comparison of SDNN values in patients with congenital heart disease

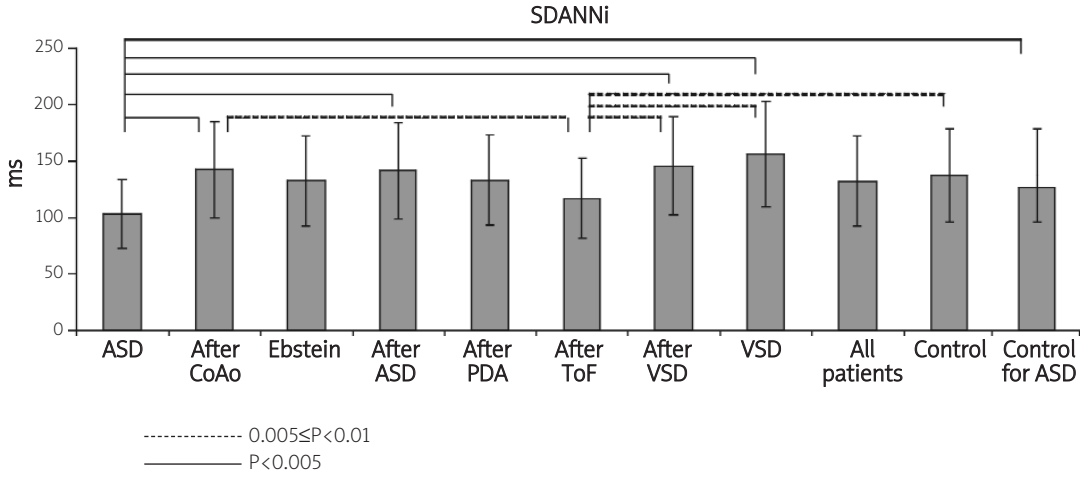

Figure 2. Comparison of SDANNi values in patients with congenital heart disease

Table I. Values of heart rate variability parameters in all subjects

	All patients	ASD	Control for ASD	After CoAo	Ebstein	After ASD	After PDA	After ToF	After VSD	VSD	Control
Number of patients	345	40	29	78	20	36	28	71	56	16	47
Age (years)	31.4±10.8	45.2±9.9	43.1±6.7	30.9±9.9	41.0±11.4	26.8±9.2	27.9±9.5	27.7±6.9	29.2±8.7	28.7±8.9	33.2±11.3
Age at the moment of surgery (years)	9.6±7.7			10.5±7.4		13.1±10.2	8.3±6.1	7.3±4.5	9.5±9.3		
SDNN (ms)	144.8±42.5	112.1±35.0	138.6±27.3	155.2±40.6	146.1±50.6	151.2±47.3	145.4±33.8	132.4±32.2	158.2±44.7	167.1±39.7	149.5±33.1
SDANNi (ms)	132.4±43.5	102.8±33.5	125.6±27.8	142.2±40.9	132.7±48.8	141.5±51.3	133.1±34.9	117.1±34.4	146.0±46.2	156.6±40.3	137.2±13.9
SDNNi (ms)	60.4±20.9	42.3±12.8	54.3±11.3	66.7±20.9	62.2±20.1	69.9±30.7	59.1±11.6	53.5±15.6	63.5±18.5	74.5±17.0	60.5±16.1
RMSSD (MS)	39.4±24.6	26.8±14.8	28.8±9.4	43.2±17.4	42.1±18.9	41.5±21.7	37.1±12.9	35.7±14.5	44.2±46.6	46.8±15.2	34.9±14.9
pNN50 (%)	14.4±11.5	6.41±8.5	7.8±6.4	18.1±12.5	15.4±11.8	14.8±12.3	14.1±9.8	12.6±10.2	14.5±10.6	22.4±11.3	12.6±10.5

ASD – persistent atrial septal defect type II
after CoAo – after correction of coarctation of aorta
Ebstein – Ebstein anomaly
after ASD – after ASDII closure
after PDA – after patent ductus arteriosus closure
after ToF – after total correction of tetralogy of Fallot
after VSD – after ventricular septal defect closure
VSD – ventricular septal defect
SDNN – standard deviation of sinus RR intervals
SDANNi – standard deviation of the means of all RR intervals for all 5-minute segments of the entire recording
SDNN-i – mean of the standard deviations of all filtered RR intervals for all 5-minute segments of the analysis
r-MSSD – root of mean of squares of RR differences
pNN50 – percentage of differences greater then 50 ms between adjacent sinus RR intervals

several time domain indexes of HRV were analysed: SDNN (standard deviation of all normal RR intervals in the entire 24-hour ECG recording), SDANN-i (standard deviation of the average normal RR intervals for all 5-minute segments of a 24-hour ECG recording), SDNN-i (mean of the standard deviations of all normal RR intervals for all 5-minute segments of a 24-hour ECG recording), r-MSSD (root-mean-square successive difference- the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-hour ECG recording), pNN50 (percentage of differences between adjacent normal RR intervals that are >50 ms computed over the entire 24-hour ECG recording). All of the Holter recordings were reanalysed using a high performance digital computer station for identifying each QRS (Oxford Excel-2, v. 7.5). After the computer had automatically detected and labelled each QRS, the data file was reviewed and edited by a cardiologist. Measurements were conducted according to the ESC and NASPE guidelines [26].

Data were presented as mean ± standard deviation (x±SD). Data distribution was estimated by Shapiro-Wilk test, and was normal. Homogeneity of variances was confirmed using Levene's test. Relationships were evaluated using Spearman rank correlation coefficients. Comparisons between groups were performed with ANOVA variance analysis. Statistical significance was considered when $p.<0.05$.

Software used: STATISTICA for Windows (license nunmber 6097048609D519).

Results

The demographic analysis of the studied population is shown in Table 1, together with time domain indexes of HRV (SDNN, SDANNi, SDNNi, rMSSD, pNN50). All analysed HRV parameters were not different in CongHD comparing to the control group.

Comparison of each of the assessed time domain HRV index among investigated population of CongHD and control group is shown in Figures 1-5. Patients with ASD II, who were much older than others in CongHD are compared to a separate "older" control group.

Correlation of patients' age and individual time domain indexes of HRV in all groups are presented in Table II. Table III shows correlations between individual time domain indexes of HRV and age at operation in all examined groups.

Discussion

HRV analysis has become a recognized diagnostic tool in the assessment of autonomic nervous system influence on the sinus node function [8-10]. Although HRV imprecisely illustrates the so called cardio-vascular stress [26] and does not correlate unequivocally with hemodynamic parameters [8, 9,

Table II. Correlation between the age of patients and HRV parameters

	All patients	ASD	After CoAo	Ebstein	After ASD	After PDA	After ToF	After VSD	VSD	Control
N	345	40	78	20	36	28	71	56	16	47
SDNN (ms)	r=-0.177 p=0.0009	NS	NS	NS	NS	NS	NS	NS	NS	-0.385 0.007
SDANNi (ms)	r=-0.156 p=0.003	NS	NS	NS	NS	NS	NS	NS	NS	-0.404 0.004
SDNNi (ms)	r=-0.319 p=0.0001	-0.3249 0.03	-0.322 0.003	NS	NS	NS	-0.265 0.02	-0.273 0.04	NS	-0.464 0.0009
rMSSD (ms)	r=-0.279 p=0.0001	NS	-0.326 0.003	NS	NS	NS	-0.250 0.03	-0.260 0.05	NS	-0.522 0.0002
pNN50%	r=-0.297 p=0.0001	NS	-0.330 0.003	NS	NS	NS	-0.257 0.03	NS	NS	-0.578 0.0001

Table III. Correlation between the age at the moment of surgery and HRV parameters

	All patients	After CoAo	After ASD	After PDA	After ToF	After VSD
N	269	78	36	28	71	56
SDNN (ms)	NS	NS	NS	NS	NS	NS
SDANNi (ms)	NS	NS	NS	NS	NS	NS
SDNNi (ms)	r=-0.163 p=0.007	-0.312 0.005	NS	NS	NS	NS
rMSSD (ms)	NS	-0.354 0.001	NS	NS	NS	-0.310 0.02
pNN50 (%)	NS	-0.41 0.0001	NS	NS	NS	-0.336 0.01

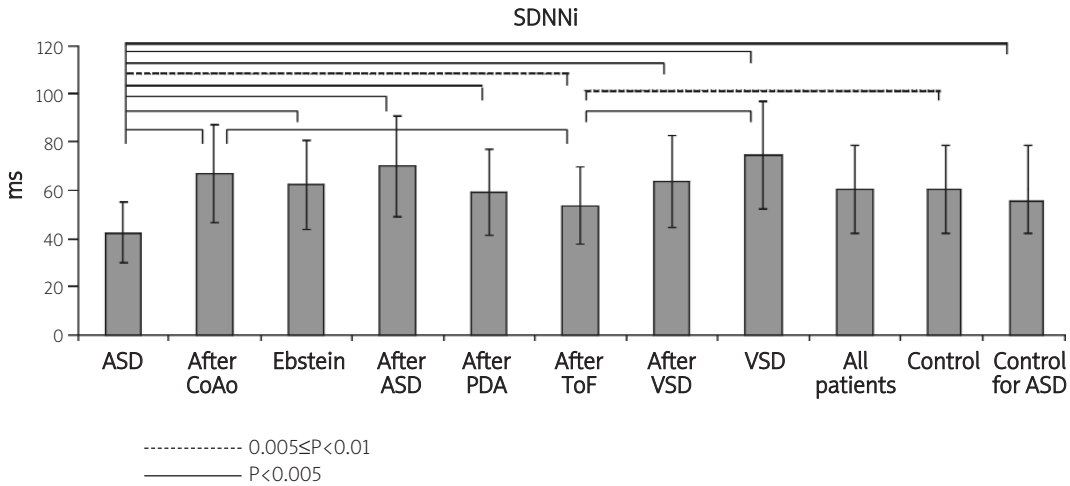

Figure 3. Comparison of SDNNi values in patients with congenital heart disease

12, 16], nor to the NYHA class in most patients [8, 9, 12], it was proved that decreased HRV values are independent prognostic factors in many disease entities [2-8, 10-14]. Simultaneously, there is a search for prognostic factors in expanding population of adult patients with congenital heart disease [16, 18-20, 25]. In our studied CongHD group, HRV parameters were not different from those in controls. A simmilar observation was made by Heraugi and Scott [26], Massin and von Bernuth [16]. They did not find decreased HRV parameters only in CongHD patients with preserved left ventricle function. Opposite results were published by Kucharska et al. [18]. It must be mentioned that the

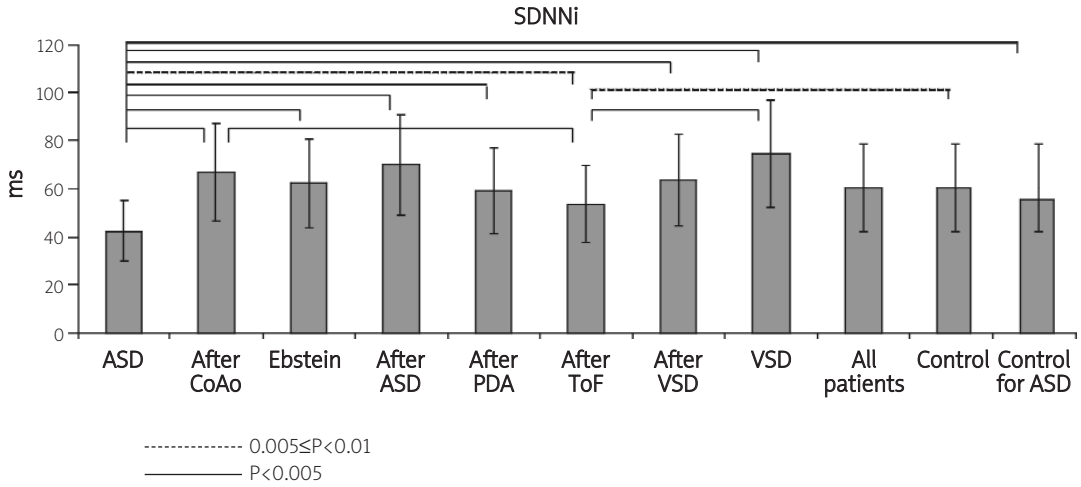

Figure 3. Comparison of SDNNi values in patients with congenital heart disease

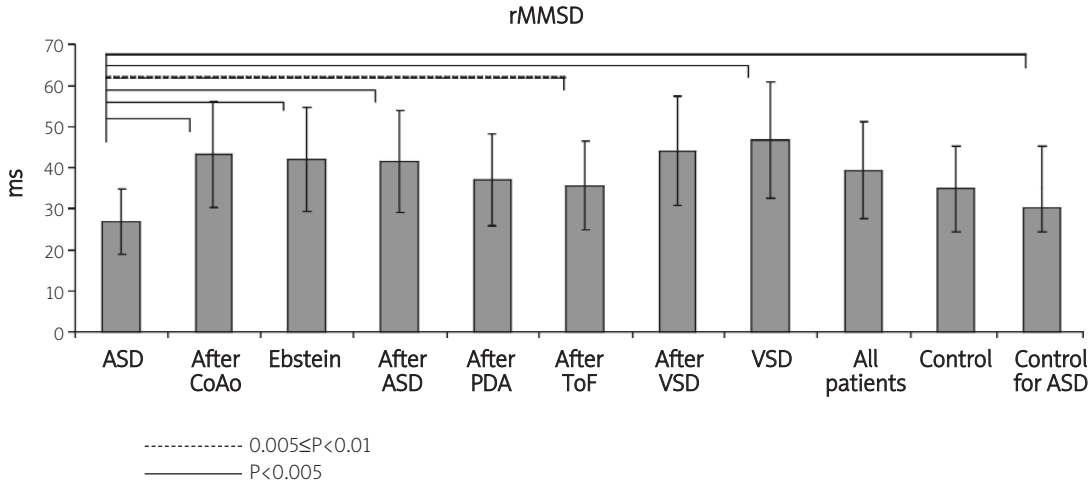

Figure 4. Comparison of rMMSD values in patients with congenital heart disease

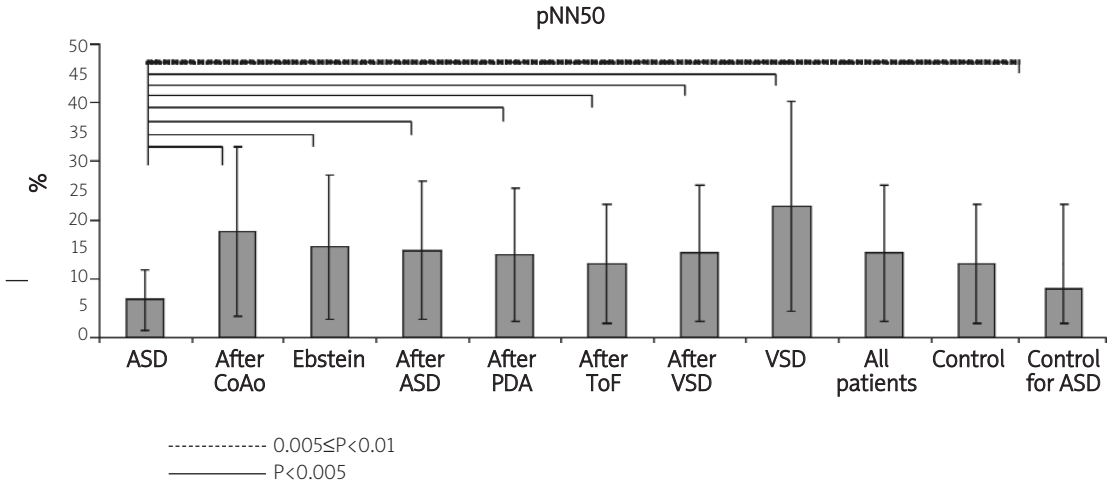

Figure 5. Comparison of pNN50 values in patients with congenital heart disease

cited studies were conducted in children. The study by Ohuchi et al. [21], including 297 pts with CongHD, 107 over 18 years of age, has shown that HRV values were decreased comparing to the healthy controls, but were similar despite the CHF stage. This finding is different from the results in populations, in which CHF is of other origin than CongHD [10, 27].

Among all analysed subgroups, only pts with ASD II and after correction of Fallots' tetralogy presented with lower HRV parameters compared to healthy subjects. This observation is consistent with the other reports [6, 18, 19, 21, 22, 28, 29]. It has to be emphasised that in this study we matched a proper control group for ASD II patients. The reason for the above observation is not fully revealed. In patients with ASD II there is not a physiologic increase in heart rate during inspiration, which is due to the lack of volume change of right atrium communicated with the left atrium [22, 29]. Apart from pressure and volume overload observed in many CongHD [16, 20, 25] in the corrected tetralogy of Falot HRV decrease is caused by autonomic fibers injury during operation [28,30], extracorporeal circulation induced myocardial ischemia [31], and systolic dysfunction of both ventricles as an effect of the pulmonary valve insufficiency. [6, 28, 32]. McLeod et al. [19] yet failed to prove correlation of the HRV values and left ventricle function in this group of patients. However, they discovered their decrease due to worsening of right ventricle hemodynamics (size, endiastolic pressure and radionuclide defined ejection fraction). Long-term observations indicate that especially patients after ToF, are at danger of lethal ventricular arrhythmia [6, 28, 32, 33]. An increase in sympathetic stimulation and decrease of parasympathetic stimulation favor initiation of arrhythmias. [8, 9, 11, 19, 28]. The HRV assessment may then play an important role in sudden cardiac death risk stratification in this group of patients. It is interesting that HRV values in ToF patients are lower than in patients with CoAo or VSD, that is, in defects with predominantly left ventricle dysfunction.

Analyzing the HRV profile you need to consider physiologic decrease due to aging. A major decrease is seen between the second and third decades (14%), during eighties there are only 70% of values seen in twenty-year-olds [34]. Our investigation showed that two oldest groups: patients with patent ASD II and with Ebstein anomaly presented with a distinct HRV profile. The former were characterised by significantly lower values comparing to age-matched controls, the latter did not differ in any of them. It is an interesting fact that patients with essentially impaired right ventricle hemodynamics and frequent supraventricular arrhythmias as seen in Ebstein anomaly do not present HRV suppression [35]. Kupper et al. [36] proved that the HRV profile might be genetically determined, though it may not always correspond with the clinical state, which might partially explain the differences mentioned above. At the same time no physiological HRV relationship with age was observed in both these groups [8, 9, 17, 26]. This age-dependence of HRV was observed, however, in whole CongHD group, and in some parameters in groups after correction of CoAo, ToF and VSD, but surely the number of patients in subgroups was of importance.

The cardiothoracic surgery was performed in 269 patients. In the analysis, it seems that this group does not reveal any relation between HRV and age at operation (negative correlation in merely one parameter). No relationship between HRV and age at operation was found in patients after correction of ASD, PDA and ToF in contrary to after CoAo and VSD group where a negative correlation was found. This may suggest a favorable effect of an earlier operation in the latter groups (CoAo, VSD), that is in conditions where the left ventricle is particularly impaired. Long-time volume overload (VSD) like pressure overload (CoAo) inevitably leads to cardiac remodelling accompanied by a decrease in HRV values [5, 10, 11, 14]. Coartcation of the aorta, is additionally accompanied by hypertension, which duration and intensity influence the autonomic system and HRV consequently [14, 15]. Cardiac surgery is to prevent these complications, and there is a general agreement that an early operation in CongHD patients determines a better prognosis [16]. Lack of HRV relation to the age at operation in remaining analysed defects may be explained as follows: early closure of PDA prevents myocardial injury [37], correction of defects resulting mainly in right ventricle dysfunction does not prevent fluctuations of the autonomic system modulation or this procedures cause essential operation stress [22, 28, 30, 31]. In ToF repaired patients decreased HRV values are a result of anatomical residua as well as surgical sequel [6, 32, 33].

Evolutions of HRV analysis raise hopes to identify patients who should receive an early antiarrhythmic and antiremodeling therapy [8, 9, 16]. Based on this evidence, HRV analysis may be useful in CongHD patients at high risk of arrhythmias, sudden cardiac death and early CHF progression.

Conclusions

1. Despite slight differences in between subgroups of CongHD patients, HRV values in adult patients with CongHD are similar to healthy population, and gradual, physiologic decrease due to aging is also present.
2. Age at operation does not influence the HRV profile in a general population of patients with CongHD. Age at operation influences HRV in patients with left ventricle overload. Similar relations are not observed in group with impaired right ventricle hemodynamics.

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