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Evaluation of exercise capacity with cardiopulmonary exercise test and B-type natriuretic peptide in adults with congenital heart disease

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Abstract

Background: *Adult patients with congenital heart disease (CHD) usually find their exercise capacity satisfactory. However, objective evaluation is important for diagnostic and prognostic purposes. The aim of this study was to evaluate exercise capacity using cardiopulmonary exercise tests and measurement of serum B-type natriuretic peptide (BNP) levels in adult patients with CHDs, both in the entire study cohort and in subjects with individual types of cardiac lesions, as well as to verify the relation between BNP level and cardiac performance.*

Methods: *The study group included 265 patients (136 males; mean age 34.4 ± 11.6 years) 173 of whom were operated on at the mean age of 9.2 ± 7.3 years. They represented the following types of CHD: 72 patients — surgically corrected coarctation of the aorta, 62 — surgically corrected tetralogy of Fallot, 28 — Ebstein anomaly, 26 — patent atrial septal defect, 24 — Eisenmenger syndrome, 20 — uncorrected or palliated complex cyanotic lesions, 11 — corrected transposition of the great arteries (TGA), 14 — TGA after Senning operation, and 8 — common ventricle after Fontana operation. The control group consisted of 39 healthy individuals (17 males) with a mean age of 35.8 ± 9.3 years.*

Results: *According to NYHA classification, 207 patients were recognized as representing class I symptoms, 47 subjects class II, and 11 class III. Cardiopulmonary exercise revealed significantly reduced exercise capacity in adults with CHD in general, compared to control subjects: maximal oxygen uptake (VO_2max) was 23.3 ± 6.9 vs. 33.6 ± 7.2 mL/kg/min, respectively (p = 0.00001); maximum heart rate at peak exercise (HRmax) —161.1 ± 33.2 vs. 179.6 ± 12.3 bpm (p = 0.00001); respiratory workload (VE/VCO_2slope) — 35.7 ± 9.7 vs. 26.3 ± 3.1 (p = 0.00001); and forced vital capacity (FVC) — 3.8 ± 1.1 vs. 4.6 ± 0.7 L (p = = 0.00003). Various degrees of peak VO_2max reduction were observed across the spectrum of CHD. Patients after repair of aortic coarctation demonstrated the highest VO_2max (26.8 ± ± 6.6 mL/kg/min), and the lowest was demonstrated by patients with Eisenmenger syndrome (12.8 ± 4.8; ANOVA p = 0.00001). Serum BNP levels in the study group were higher than in*

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the controls: 55.4 ± 67.5 vs. *13.9 ± 13.7 pg/mL, respectively (p = 0.00001). Various degrees of BNP level increase were found across the spectrum of CHD. Patients after repair of aortic coarctation demonstrated the lowest BNP level (24.8 pg/mL), and the highest level was found in patients with cyanotic defects (120.7 pg/mL; ANOVA p = 0.00001). BNP levels across the NYHA classes were as follows: I — 35.7 pg/mL, II — 94.1 pg/mL, and III — 225.6 pg/mL. BNP levels showed negative correlation with VO_2max (r = –0.525, p = 0.0001), FVC (r = = –0.349, p = 0.00001), FEV_1 (r = –0.335, p= 0.00001), and positive correlation with VE/VCO_2slope (r = 0.447, p = 0.00001).*

Conclusions: *The exercise capacity of patients with CHD is, in general, compromised, most strikingly in patients suffering from pulmonary hypertension and cyanosis. Serum BNP levels in these subjects are increased and correlate well with exercise capacity. BNP level is higher in patients with cyanotic CHDs.* (Cardiol J 2009; 16, 2: 133–141)

Key words: cardiopulmonary exercise testing, congenital heart disease, natriuretic peptide type B

Introduction

As a result of long-term adaptation, adult patients with congenital heart disease (CHD) usually self-report their exercise capacity as satisfactory [1–5]. However, heart failure (HF) remains the major clinical problem in this group of patients. The pathophysiology of heart failure in adults with CHD is complex, with primary causes related to impairment of both left and/or right ventricular function, as well as to great vessel abnormalities [1, 6–14]. Pulmonary hypertension often adds to or affects the pathophysiology of heart failure [10, 12, 15]. Thus, the assessment of heart failure severity in such a clinically diverse population is quite difficult, but still necessary as it has important therapeutic implications [2, 3, 10, 12, 16, 17]. It has been shown that, similarly to patients with left ventricular heart failure [18], cardiopulmonary exercise testing is also an objective diagnostic and prognostic tool in adult patients with CHDs [1, 10, 12, 19–21]. B-type natriuretic peptide (BNP) concentration is another validated diagnostic and prognostic marker of heart failure [19, 22]. Recently, the diagnostic relevance of BNP in certain types of CHD has been shown [6, 10, 17, 23–28]. However, we are not aware of any reports on the relationship between serum BNP levels and cardiac performance determined by means of cardiopulmonary exercise test in the general population of adult patients with CHD.

The aim of this study was to evaluate exercise capacity in adults with CHD using cardiopulmonary exercise testing, and measurement of serum BNP levels in the entire study cohort and in patients with different types of cardiac lesions. Additionally, the possible correlations between BNP levels and cardiac performance were explored.

Methods

The study group was selected from the population of patients followed-up at the Congenital Heart Disease Outpatient Clinic of the 1st Department of Cardiology of the Medical University of Poznan. It consisted of 265 patients (136 males) aged 19–65 years (mean 34.4 ± 11.6 years); 173 (65.3%) of them were operated on at the age of 1–42 years (mean 9.2 ± 7.3 years), 9–34 years earlier (mean 21.8 ± 7.4 years). In Table 1, the clinical characteristics of the group are detailed; the study cohort included: 72 patients with surgically corrected coarctation of the aorta (CoAo), 62 patients with surgically corrected tetralogy of Fallot (ToF), 28 patients with Ebstein anomaly, 26 patients with patent atrial septal defect (ASD), 24 patients with Eisenmenger syndrome, 20 patients with uncorrected or palliated complex cyanotic lesions (ToF, transposition of the great arteries, double inlet left ventricle, tricuspid atresia), 11 patients with corrected transposition of the great arteries, 14 patients with transposition of the great arteries after Senning operation, and 8 patients with common ventricle after Fontana operation. In 53 (20.0%) patients, arterial blood oxygen saturation (SO_2) was below 90%. Pulmonary hypertension, found on echocardiography (right ventricular end-systolic pressure > 30 mm Hg), was confirmed in 58 subjects (21.9%). None of the patients was in the early

Table 1. Demographic and clinical characteristics of analyzed group of patients.

Congenital heart diseases	No. of patients	Gender of male (%)	Age (years)	No. of operated on	Age at time of surgery (years)	NYHA class I/II/III
Operated coarctation of aorta	72	44 (61%)	32.5 ± 10.4	72 (100%)	10.6 ± 8.9	70/2/0
Ebstein anomaly	28	21 (75%)	39.4 ± 11.8	0	–	26/3/1
Tetralogy of Fallot	62	32 (51.6%)	29.7 ± 9.3	62 (100%)	7.6 ± 4.9	60/1/1
Atrial septal defect	26	10 (38.5%)	43.2 ± 8.9	0	–	26/0/0
Eisenmenger syndrome	24	5 (20.8%)	44.1 ± 14.1	0	0	0/19/6
Complex cyanotic lesions	20	10 (50.0%)	33.6 ± 11.1	14 (70.0%)	12.3 ± 11.4	2/13/5
TGA after Senning operation	14	6 (42.8%)	26.1 ± 14.8	14 (100%)	4.3 ± 3.8	12/2/0
Corrected TGA	11	6 (54.5%)	36.1 ± 12.1	3 (27.3%)	20.6 ± 11.2	6/5/0
Common ventricle after Fontan operation	8	2 (25%)	23.8 ± 3.8	8 (100%)	8.7 ± 3.1	5/2/1

TGA — transposition of the great arteries

postoperative period. The control group comprised 39 healthy individuals (17 males) aged 23–58 years (mean 35.8 ± 9.3 years). New York Heart Association (NYHA) functional class was determined based on clinical evaluation and the patient's self-reported symptoms at the time of the exercise test. All patients had a sinus rhythm (patients with atrial fibrillation/flutter were excluded); neither arrhythmia nor pulmonary disease were found in these patients, serum creatinine levels were below 140 μg/ml, and aspartate aminotransferase levels did not exceed twice the upper limit of the normal.

Some patients were on diuretics and ACE-inhibitors, and 3.7% of patients were on beta-blockers, which were continued at the time of study for ethical reasons. Arterial hypertension was diagnosed in 29 patients.

Laboratory analysis

In all patients, blood samples were drawn from an antecubital vein prior to the exercise test after a 15 min rest in supine position. The concentrations of brain natriuretic peptide in human serum were determined with the use of immunoradiometric assay kit — Shionoria BNP (Schering CIS bio international). The radioactivity was measured for 1 minute with a gamma scintillation counter type NZ 335.

Cardiopulmonary exercise test

All patients carried out a maximal, symptom-limited (fatigue and/or dyspnea) treadmill exercise test according to modified Bruce protocol (adding to standard Bruce protocol stage 0–3 min; 1.7 km/h, at 5% grading), whereas the control subjects tests were carried out according to standard Bruce protocol. Patients were encouraged to continue with the test for as long as their respiratory quotient exceeded one. The maximal oxygen consumption (peakVO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured using breath by breath gas analysis (Sensor Medics, model Vmax29). The system was calibrated with a standard gas mixture of known concentrations before each test. A standard 12-lead electrocardiogram was continuously recorded. Blood pressure was measured every two minutes using a cuff sphygmomanometer. Peak VO_2 was defined as a mean of values measured within the last 20 s of exercise, and expressed as both mL/kg/min and mL/min, and as the percentage of predicted peak oxygen consumption. The ventilation/carbon dioxide slope (VE/VCO_2slope) was calculated automatically by computer system Vmax29. Spirometry was performed in all subjects before cardiopulmonary exercise test with measurement of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), and was calculated as a percentage of the predicted values, adjusted for age, sex, and body mass. The evaluation of the cardiopulmonary exercise test was performed by investigators that were blinded to the results of the BNP measurements.

Statistical analysis

Continuous variables following normal distribution were expressed as mean and standard deviation, and those not normally distributed as median and range. Variables following normal distribution were compared using *t*-Student test for unpaired samples. Otherwise, the Mann-Whithney U test was used. For comparisons involving more than

Table 2. Comparison of cardiopulmonary exercise test parameters and brain natriuretic peptide (BNP) levels between studied patients and control group.

	Study group (n = 265)	Control group (n =39)	P
Age (years)	34.4 ± 11.6	35.8 ± 9.3	0.20
BNP [pg/mL]	55.4 ± 67.5	13.9 ± 13.7	0.00001
SO_2 (%)	94.8 ± 7.3	99.1 ± 0.9	0.00001
VO_2 [mL/kg/min]	23.3 ± 6.9	33.6 ± 7.2	0.00001
VO_2%	62.0 ± 15.9	88.9 ± 14.8	0.00001
VE/VCO_2	35.7 ± 9.7	26.3 ± 3.1	0.00001
HRmax [bpm]	161.1 ± 33.2	179.6 ± 12.3	0.00001
HRmax%	88.0 ± 13.2	100.1 ± 7.2	0.00001
FVC [L]	3.8 ± 1.1	4.6 ± 0.7	0.00003
FVC%	90.2 ± 17.5	103.2 ± 9.1	0.00001
FEV_1 [L]	3.0 ± 0.8	3.7 ± 2.4	0.00001
FEV_1%	81.6 ± 21.6	99.2 ± 10.7	0.00001
BPmax [mm Hg]	165.5 ± 26.5	170.6 ± 15.3	0.05
Respiratory quotient	1.06 ± 0.05	1.1 ± 0.07	0.0007

SO_2 — saturation, VO_2 — peak oxygen consumption, VE/VCO_2slope — ventilatory equivalent for carbon dioxide, FVC — forced vital capacity, FEV_1 — forced expiratory volume in one second, BPmax — peak exercise blood pressure, HRmax — peak exercise heart rate

two groups, ANOVA with Tukey *post-hoc* test following Shapiro-Wilk test for normality and Leven's test for homogeneity of variance or Kruskal-Wallis test with Dunn's multiple comparisons test were used. To assess the degree of correlation between variables, Spearman's Rank Correlation or Pearson's Correlation statistics (depending on variable distribution) were used. Results are presented as the coefficient of correlation (r). A p value < 0.05 was considered significant. Statistical analysis was carried out using Statistica software rev. 8.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a *priori* approval of the institution's human research committee.

Results

Among all the study patients, 207 (78.1%) self-assessed their exercise capacity as satisfactory (NYHA I), 47 (17.7%) as moderately limited (NYHA II), and the remaining 11 (4.1%) as significantly compromised (NYHA III).

Cardiopulmonary exercise test results are summarized in Table 2. In the general group of CHD adults, VO_2max and VO_2max% was significantly lower then measured in the control group ($p = = 0.00001$ and $p = 0.00001$, respectively). The maximum heart rate at peak exercise was significantly lower than in the healthy individuals ($p = 0.00001$ and $p = 0.00001$, respectively). The peak systolic blood pressure was higher in the control group ($p = 0.05$). A significant difference was observed with respect to the index of the respiratory workload (VE/VCO_2slope), which was higher in the study group than in the controls ($p = = 0.00001$). The main respiratory quotient in the analyzed patients was significantly lower than in the controls ($p = 0.0001$).

Spirometry

Values of pulmonary elasticity parameters, FVC and FVC%, were lower in patients with CHD than in the control group ($p = 0.00003$ and $p = 0.00001$, respectively). Moreover, markers of airway obstruction, FEV_1 and FEV_1%, were significantly lower than in the control group ($p = 0.00001$ and $p = 0.00001$, respectively).

The impact of cardiac lesion type on exercise capacity: a varying degree of peak VO_2 reduction (expressed as mL/kg/min, mean ± SD) was found across the spectrum of congenital heart disease types (Fig. 1). Patients after repair of the aortic coarctation demonstrated the highest peak oxygen consumption (26.8 ± 6.6). Lower VO_2 was observed in patients with corrected ToF (24.9 ± 5.7), patent ASD (24.6 ± 4.8), corrected transposition of the great arteries (24.2 ± 6.6), Ebstein anomaly (22.3 ± ± 5.0), transposition of the great arteries after Senning surgery (21.1 ± 5.9), common ventricle after Fontan operation (19.5 ± 3.8) and complex cyanotic

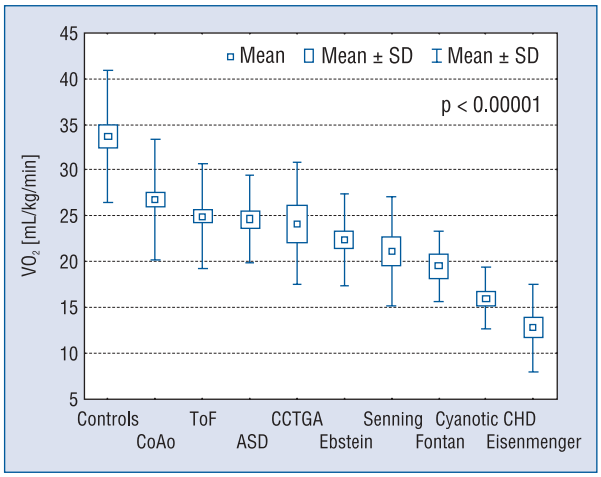

Figure 1. Maximum oxygen uptake (VO_2) for each congenital heart disease; CoAo — coarctation of aorta, ToF — operated tetralogy of Fallot, ASD — patent atrial septal defect, CCTGA — corrected transposition of the great arteries, Ebstein — Ebstein anomaly, Senning — transposition of the great arteries after Senning operation, Fontan — common ventricle after Fontan operation, cyanotic CHD — cyanotic congenital heart diseases, Eisenmenger — Eisenmenger syndrome.

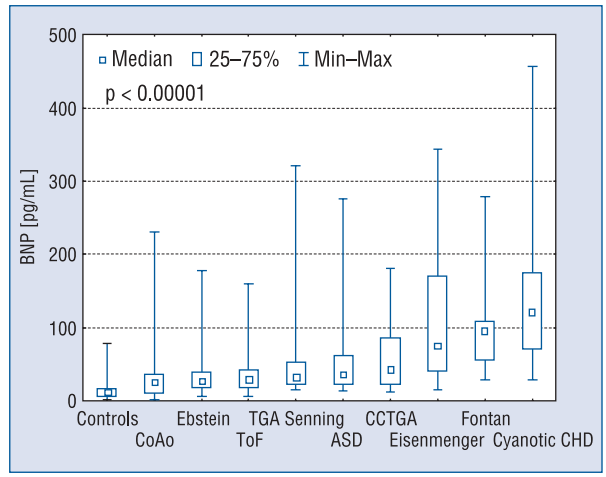

Figure 2. Serum brain natriuretic peptide (BNP) levels in each congenital heart disease (for abbreviations see Fig. 1).

lesions (15.9 ± 3.4), and the lowest VO_2 was seen in patients with Eisenmenger syndrome (12.8 ± ± 4.8; ANOVA p = = 0.00001). These differences remained significant after inclusion of age as a possible confounder in an ANCOVA (p = 0.0001). Significant differences in VO_2 were observed between individuals with Eisenmenger syndrome and CoAo (p = 0.00001), corrected ToF (p = 0.00001), Ebstein anomaly (p = 0.00003), ASD (p = 0.00001), corrected transposition of the great arteries (p = 0.0003), transposition of the great arteries after Senning operation (p = 0.003) and between complex cyanotic lesions and CoAo (p = 0.00002), corrected ToF (p = 0.0007), ASD (p = 0.001), and corrected transposition of the great arteries (p = 0.03).

Serum BNP levels in the study group were higher than in controls: 55.4 ± 67.5 *vs*. 13.9 ± ± 13.7 pg/mL (p = 0.00001). They did not exceed the commonly recognized normal value of 100 pg in 226 patients (85.3% of the study population).

The impact of cardiac lesion type on serum BNP concentration: A varying degree of serum BNP level increase (expressed as pg/ml and median, range) was found across the spectrum of congenital heart disease types (Fig. 2). Patients after repair of aortic coarctation demonstrated the lowest BNP level (24.8; 1.4–299.9); higher concentrations of this peptide were seen in patients with Ebstein anomaly (26.7; 5.2–178.2), after correction of ToF (29.3; 6.2–159.4), transposition of the great arteries after Senning operation (32.8; 15.2–321.4), ASD (35.7; 13.8–276.1), corrected transposition of the great arteries (42.1; 11.3–180.2), Eisenmenger syndrome (75.6; 14.2–343.9), after Fontan surgery (95.5; 27.9–278.8), and in patients with complex cyanotic disease (120.7; 28.8—456.5; ANOVA p = 0.00001). These differences remained significant after adjusting for age (ANCOVA p = 0.0001). Significant differences in BNP concentrations were observed between Eisenmenger syndrome and CoAo (p = 0.00001), repaired ToF (p = 0.006), and Ebstein anomaly (p = 0.02), as well as between complex cyanotic defects and the latter three (p = 0.00003, p = 0.0008, p = 0.002, respectively).

Serum BNP increased, along with the severity of heart failure (Fig. 2), being 35.7 pg/mL in NYHA I individuals, 94.1 pg/mL in NYHA II, and 225.6 pg/mL in the most symptomatic patients. There were significant differences between BNP level in NYHA I *vs*. NYHA II patient groups and between NYHA I *vs*. NYHA III patient groups (p = = 0.00001, p = 0.00001)

Analysis of serum BNP levels and cardiopulmonary exercise test parameters revealed a negative correlation between BNP levels and peak oxygen uptake VO_2max (r = –0.525, p = 0.0001), FVC (r = –0.349, p = 0.00001), and FEV_1 (r = –0.335, p = 0.00001); a positive correlation was observed between BNP levels and VE/VCO_2 slope (r = 0.447, p = 0.00001) (Fig. 3–6). No significant correlations between BNP concentration and current patient age and age at time of operation were found.

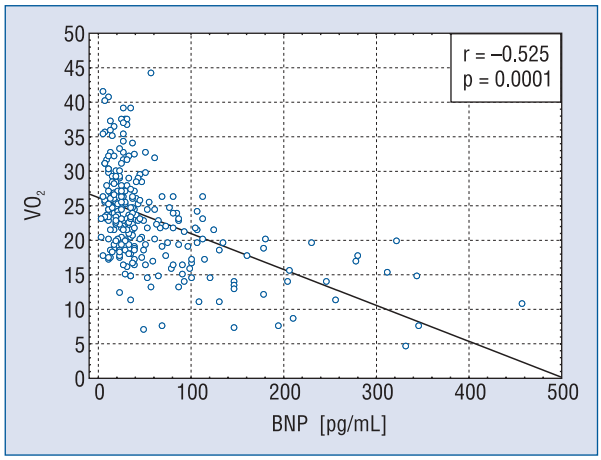

Figure 3. Correlation between BNP levels and VO_2max in patients with congenital heart disease.

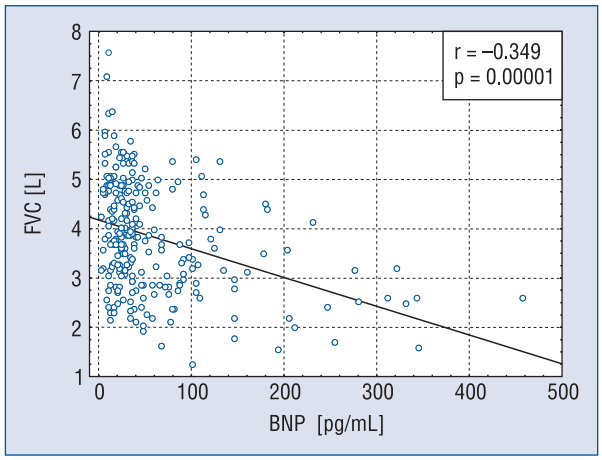

Figure 5. Correlation between BNP levels and FVC in patients with congenital heart disease.

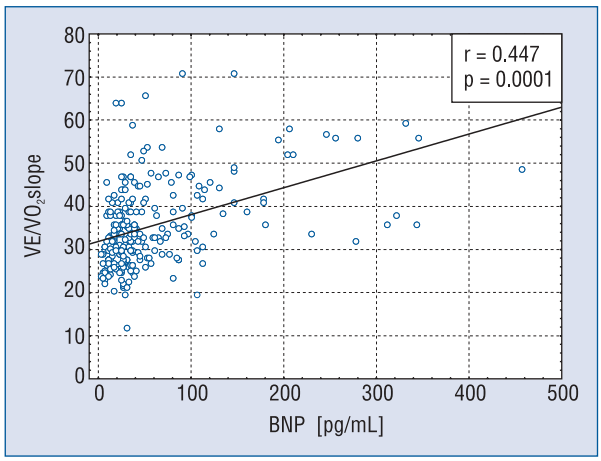

Figure 4. Correlation between BNP levels and VE/VCO_2 slope in patients with congenital heart disease.

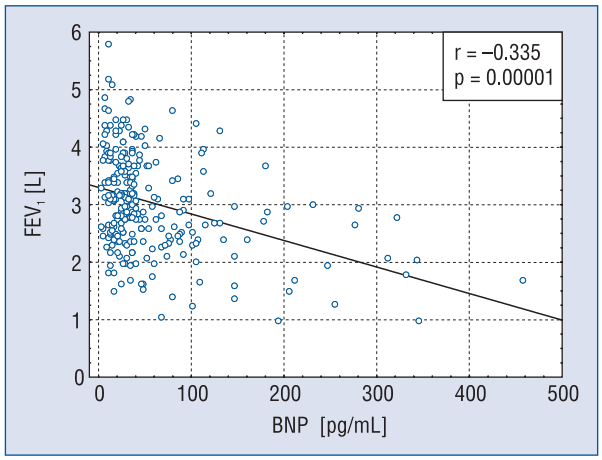

Figure 6. Correlation between BNP levels and FEV_1 in patients with congenital heart disease.

Discussion

The majority of study patients with CHD were asymptomatic or presented with minor signs of heart failure. As many as 17.7% of subjects had NYHA class II symptoms, and only 4.1% had NYHA class III. Such a good subjective appraisal of exercise capacity in this population remains consistent with our previous observations [2–5] as well as with the reports of other investigators [1, 29]. However, true exercise capacity in our patients was significantly compromised, similarly to the findings reported in recently published studies [1, 7, 10, 14, 19, 30]. The mechanism of heart failure in adults with CHD is complex, depending on the severity of cardiovascular disease, concomitant pulmonary pathology, and the presence of cyanosis, myocardial damage resulting from inadequate protection during cardiac surgery, arrhythmia, neurohormonal activity, and comorbidities such as ischemic heart disease or hypertension [1, 7–13, 15, 31]. Our study showed that heart failure was less pronounced in patients after repair of coarctation of the aorta, marked in subjects with cyanotic defects, and most severe in subjects with Eisenmenger syndrome; this is also consistent with observations reported by Royal Brompton Hospital investigators [19]. Similar analysis reported by Fredriksen et al. [1] suggested the lowest exercise capacity in patients with heart of single ventricular physiology, and the highest capacity in patients after correction of ToF; this study, however, lacked patients with corrected coarctation of the aorta and subjects with secondary pulmonary hypertension. Diller et al. [19] showed

that most significant predictors of poor maximum oxygen consumption are low maximum heart rate at peak exercise, low forced expiratory volume in one second, high NYHA functional class, and, most of all, the presence of pulmonary hypertension and cyanosis. This may explain our finding of most severe heart failure in patients with Eisenmenger syndrome. Due to the anatomical complexity of congenital heart disease and the pathomechanisms of resultant heart failure causing diagnostic problems, investigators are looking for reliable and easily accessible diagnostic and prognostic markers in adults with CHD. The previously-mentioned investigators from London [19] suggested that maximum oxygen consumption may serve as such a marker, documenting increased risk of hospitalization and mortality if less than 15.5 mL/kg/min. This criterion was met by 32 of our patients (12.2%). Dimopoulos et al. [13] reported ventilatory equivalent ratio for carbon dioxide (VE/VCO_2slope) above 38 to be a risk factor of mortality in adults with non-cyanotic CHD. In our study 48 (22.6%) of 212 such selected patients met that criterion. In the majority of adults with CHD, reduced chronotropic response significantly affected heart failure prevalence [1, 11, 20, 30]. According to Diller et al. [14] failure to reach 80% of age- and sex-adjusted predicted maximum heart rate at peak exercise is another risk factor of mortality in this population. In our cohort, 57 patients (21.6%) did not reach such a heart rate threshold. Our analyses showed that despite self-reported good general feeling, about 1/5 of patients with CHD were at high risk of mortality.

Another diagnostic and prognostic risk factor in heart failure is serum concentration of B-type natriuretic peptide. Increased BNP level is the result of increased heart chamber wall stress, resulting form increased blood volume typical of heart failure [10, 32, 33]. Other stimuli for BNP secretion have been documented to be pulmonary hypertension and cyanosis [34–37]. Our group of CHD patients had high BNP levels, significantly exceeding those in healthy controls; however, most of them did not exceed the accepted normal value. According to published data BNP levels are increased in most types of CHD with both volume and pressure overload of left [5, 24, 38] or right ventricles [16, 17, 23, 27, 28, 35, 39] as well as of the single ventricular heart [17, 29, 39].

Analysis has shown significant correlation between serum BNP and cardiopulmonary exercise test parameters, namely maximum oxygen consumption (VO_2max) and ventilation to perfusion ratio (VE/VCO_2slope). A similar relationship between BNP and above mentioned parameters was confirmed in patients after total repair of tetralogy of Fallot [3]. Other investigators found, in a similar group of patients, significant correlation between BNP levels and maximum oxygen consumption [40]. This association was also confirmed in our analyses in adults with patent ASD [2]. Bolger et al. [6] came to similar conclusions in various types of CHD in adults. However, an association between BNP level and VO_2 was not confirmed by Dore et al. [16] in subjects with corrected transposition of the great arteries and transposition of the great arteries after Mustard operation. Our study has also shown significant negative correlation between BNP level and pulmonary elasticity (FVC) and obstruction (FEV_1) parameters. An association between B-type natriuretic hormone levels and FVC was also confirmed in patients after repair of tetralogy of Fallot [3]. Results of this observation may confirm the significant role of pulmonary pathology in the pathogenesis of heart failure in CHD adults, suggested by other authors [1, 15, 41].

At the same time, no significant correlation between BNP concentration and current patient age and age at the time of surgery was found. The early success of cardiac surgery, particularly in patients with complex heart defects, helped them to reach adulthood. However, such a group remains unprotected against progression of complications resulting from sequels as well as the consequences of the surgery performed, that both worsen heart failure with age [42].

B-type natriuretic peptide levels increased along with the severity of heart failure expressed as NYHA functional class, regardless of CHD anatomy, which is consistent with other reports [6, 24, 27, 28]. On the other hand, the anatomical background of CHD somehow influences serum BNP level. Our analysis revealed lower BNP concentration in patients with a history of repair of coarctation of the aorta, being the highest in subjects with complex cyanotic defects. In addition, the distribution resembles that of the maximum oxygen consumption profile (VO_2) in individual CHDs. There is a trend of BNP changes in various CHDs, and may result from the complexity of cardiac anomalies and progressing heart failure as a consequence.

Conclusions

1. Exercise capacity of adult patients with CHD is compromised with the highest severity in patients with defects that involve pulmonary hypertension and cyanosis.

2. Serum BNP levels in these subjects are increased and closely correlated with exercise capacity. The B-type natriuretic peptide level is highest in patients with cyanotic congenital heart disease.

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