

Evaluation of exercise capacity with cardiopulmonary exercise testing and BNP levels in adult patients with single or systemic right ventricles

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Abstract

Introduction: The aim of the study was to evaluate exercise capacity using cardiopulmonary exercise test (CpET) and serum B-type natriuretic peptide (BNP) levels in patients with single or systemic right ventricles.

Material and methods: The study group included 40 patients (16 males) – 17 with transposition of the great arteries after Senning operation, 13 with corrected transposition of the great arteries and 10 with single ventricle after Fontan operation, aged 19-55 years (mean 28.8 ±9.5 years). The control group included 22 healthy individuals (10 males) aged 23-49 years (mean 30.6 ±6.1 years).

Results: The majority of patients reported good exercise tolerance – accordingly 27 were classified in NYHA class I (67.5%), 12 (30%) in class II, and only 1 (0.5%) in class III. Cardiopulmonary exercise test revealed significantly lower exercise capacity in study patients than in control subjects. In the study vs. control group VO_{2max} was 21.7 ±5.9 vs. 34.2 ±7.4 ml/kg/min ($p = 0.00001$), maximum heart rate at peak exercise (HRmax) 152.5 ±32.3 vs. 187.2 ±15.6 bpm ($p = 0.00001$), VE/ VCO_2 slope 34.8 ±7.1 vs. 25.7 ±3.2 ($p = 0.00001$), forced vital capacity (FVC) 3.7 ±0.9l vs. 4.6 ±0.3 ($p = 0.03$), forced expiratory volume in 1 s (FEV_1) 3.0 ±0.7 vs. 3.7 ±0.9l ($p = 0.0002$) respectively. Serum BNP concentrations were higher in study patients than in control subjects; 71.8 ±74.4 vs. 10.7 ±8.1 (pg/ml) respectively ($p = 0.00001$). No significant correlations between BNP levels and CpET parameters were found.

Conclusions: Patients with a morphological right ventricle serving the systemic circulation and those with common ventricle physiology after Fontan operation show markedly reduced exercise capacity. They are also characterized by higher serum BNP concentrations, which do not however correlate with CpET parameters.

Key words: B-type natriuretic peptide, heart failure, grown up congenital heart disease, common ventricle, Senning/Mustard operation, Fontan operation.

Introduction

Patients with transposition of the great arteries after Senning/Mustard operation (TGA), those with corrected transposition of the great arteries (CCTGA) in whom a morphological right ventricle serves the systemic circulation and patients with common ventricular physiology after Fontan operation share special haemodynamic characteristics. The morphological right ventricle faces systemic circulation resistance, and thus works under

higher pressure afterload [1-6]. Single ventricle function in survivors of Fontan operation is highly dependent upon preload [7-9]. In these two clinical scenarios atrioventricular valve incompetence increasing during exercise leads to higher volume load of ventricles [9, 10]. As a result such patients often develop heart failure [4, 5, 9, 10-14]. Adult patients with congenital heart disease (CHD), due to long-term adaptation, usually self-assess their exercise tolerance as satisfactory [15-19]. Objective evaluation of exercise capacity in such patients is of key importance since the introduction of appropriate treatment during the asymptomatic phase may improve outcomes in terms of heart failure symptoms, hospitalizations and mortality. The cardiopulmonary exercise test is a validated diagnostic and prognostic tool both in patients with left ventricular heart failure [20] and in those with selected CHD [15, 21-26]. Similar diagnostic and prognostic value of serum B-type natriuretic peptide (BNP) concentrations has been documented [20], including in adult patients with CHD in whom left [16, 27-29] or right ventricular [17, 18, 21, 30-34] function is impaired as a result of pressure or volume overload. However, we are not aware of any reports on relations between BNP levels and exercise capacity measured with the cardiopulmonary exercise test in a specific population of patients with a morphological right ventricle serving the systemic circulation or common ventricular physiology after Fontan operation.

The study aimed to evaluate exercise capacity using the cardiopulmonary exercise test in adult patients with a morphological right ventricle or single ventricle serving the systemic circulation, and levels of serum BNP in these patients, and to determine the relationship between BNP concentrations and cardiopulmonary exercise test parameters.

Material and methods

Patients

The study group included 40 patients (16 males) – 17 with transposition of the great arteries after Senning operation (TGA), 13 with corrected transposition of the great arteries (CCTGA) and

10 with a common ventricle after Fontan operation, aged 19-55 years (mean 28.8 ± 9.5 years). TGA patients were operated on at the age of 1-14 years (mean 4.3 ± 3.7 years), 18-30 years earlier (mean 21.6 ± 4.2 years); 2 of them presented with small interatrial shunts. Of those with CCTGA 3 patients were operated on at the age of 11-33 years (mean 20.7 ± 11.2 years); in 1 a ventricular septal defect (VSD) was closed and tricuspid valvuloplasty was done, in another an atrial septal defect (ASD) was closed and the tricuspid valve was replaced with a mechanical prosthesis, and in the third both an ASD and VSD were closed and tricuspid valvuloplasty was carried out. The only other accompanying abnormality, found in 3 CCTGA subjects, was right ventricular outflow tract obstruction with pressure gradients not exceeding 50 mm Hg. Fontan operations in patients with common ventricular physiology were performed in subjects at the age of 5-14 years (mean 9.5 ± 3.1 years), in all cases adopting the method of right atrial to pulmonary artery connections (Table I). Arterial blood oxygen saturation was 84-99% (mean $95.2 \pm 5.0\%$) in the entire study group. The control group included 22 healthy individuals (10 males) aged 23-49 years (mean 30.6 ± 6.1 years). NYHA functional class was determined by a physician based on the assessment of patient's self-reported symptoms at the time of the exercise test. All study patients had sinus rhythm (subjects with atrial fibrillation/flutter were excluded), were free from arrhythmia and pulmonary disease and had serum creatine levels less than 140 $\mu\text{g/ml}$ and glutamic oxaloacetic transaminase activity not exceeding twice the upper limit of normal.

Measurement of serum BNP concentrations

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

Table I. Demographic and clinical characteristics of analysed group of patients

Congenital heart disease	Number of patients	Gender % male	Age [years]	Number of treated patients	Age of operation [years]	NYHA class I/II/III
TGA-Senning	17	7 (41%)	26.1 ± 4.9	17 (100%)	4.3 ± 3.7	15/2/0
CCTGA	13	6 (46%)	36.2 ± 12.1	3 (23%)	20.7 ± 11.2	6/7/0
Fontan	10	3 (33%)	23.8 ± 3.1	10 (100%)	9.5 ± 3.1	6/3/1

TGA-Senning – transposition of the great arteries after Senning operation, CCTGA – corrected transposition of the great arteries, Fontan – common ventricle after Fontan operation

Cardiopulmonary exercise test

In all study patients a maximum, symptom-limited (fatigue and/or dyspnoea) treadmill exercise test according to modified Bruce protocol was performed (standard Bruce protocol with stage 0 added – 3 min at 1.7 km/h, 5% grading), whereas in control subjects standard Bruce protocol was used. Patients were encouraged to continue walking for as long as their respiratory quotient (RQ) exceeded 1. The peak oxygen consumption (peak VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured using breath-by-breath gas analysis (Sensor Medics, model Vmax29). Before each test the system was calibrated with a standardized gas mixture. A standard 12-lead electrocardiogram was continuously recorded. Blood pressure was measured every 2 min using a cuff sphygmomanometer. Peak VO_2 represents an average value measured during the last 20 s of exercise, and is expressed as ml/kg/min, ml/min, and the percentage of predicted peak oxygen consumption. The ventilation/carbon dioxide slope (VE/VCO_2 slope) was calculated automatically by the computer system of Vmax29. A spirometric study was performed in all subjects before the cardiopulmonary exercise test, providing measurement of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), which were expressed as percentage of predicted normal values

Table II. Comparison of BNP levels and spirometric parameters between studied group of patients and control group

	Study group N = 40	Control group N = 22	Value of p
Age [years]	28.8 ±9.5	30.3 ±6.1	0.06
BNP [pg/ml]	71.8 ±74.4	10.7 ±8.1	0.00001
VO_2 [ml/kg/min]	21.7 ±5.9	34.1 ±7.2	0.00001
$\text{VO}_2\%$	54.7 ±11.3	89.5 ±15.7	0.00001
VE/VCO_2	34.8 ±7.1	25.7 ±3.2	0.00001
HR max [bpm]	152.5 ±32.3	187.2 ±15.6	0.00001
HR max %	80.9 ±16.3	97.8 ±7.7	0.00005
FVC [l]	3.7 ±0.9	4.6 ±0.3	0.03
FVC %	95.5 ±14.4	104.3 ±9.4	0.04
FEV_1 [l]	3.0 ±0.7	3.7 ±0.9	0.04
$\text{FEV}_1\%$	79.8 ±29.9	98.1 ±12.4	0.0002
BP max [mm Hg]	161.5 ±20.3	174.6 ±12.3	0.04
RQ	1.0 ±0.04	1.1 ±0.06	0.0005

BNP – brain natriuretic peptide, VO_2 – peak oxygen consumption, VE/VCO_2 slope – ventilatory equivalent for carbon dioxide, FVC – forced vital capacity, FEV_1 – forced expiratory volume in 1 s, BP max – peak exercise blood pressure, HR max – peak exercise heart rate, RQ – respiratory quotient

adjusting for age, sex and body mass. The evaluation of the cardiopulmonary exercise tests was performed by investigators blinded to the results of BNP measurements.

Statistical analysis

Continuous variables following a normal distribution were expressed as mean and standard deviation, those not normally distributed as median and range. Variables following a normal distribution were compared using Student's *t*-test for unpaired samples. Otherwise the Mann-Whitney U test was used. For comparisons involving more than 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 coefficient (depending on variable distribution) was used. Results are presented as the coefficient of correlation (*r*). *P* value < 0.05 was considered significant. Statistical analysis was carried out using Statistica software ver. 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

The majority of patients, 27 (67.5%), self-reported their exercise capacity as satisfactory and accordingly were classified as NYHA class I; 12 patients (30%) reported mild intolerance of exercise and were classified as NYHA class II; and only 1 patient (0.5%) after Fontan operation presented with symptoms of heart failure class III.

Heart failure symptoms were observed in 2 patients (12%) with TGA, 7 (54%) with CCTGA, and 4 (40%) with a single ventricle following Fontan surgery.

Cardiopulmonary exercise test parameters

As shown in Table II, the peak VO_2 was lower in the study group than in the control group (*p* = 0.00001). Maximum heart rate at peak exercise (HRmax) was also lower in the study group than in healthy individuals (*p* = 0.00001, Table II). A significant difference was also observed for the respiratory workload parameter VE/VCO_2 slope, which was higher in the study group vs. the control group (*p* = 0.00001, Table II). Among studied patients the systolic blood pressure at peak exercise was lower than in the control group (*p* = 0.04, Table II). Main respiratory quotient (RQ) in the

analysed patients was significantly lower than in the control group ($p = 0.0005$, Table II).

Spirometric study

Parameters of pulmonary elasticity FVC and FVC% were significantly lower in patients with analysed congenital heart disease than in healthy controls ($p = 0.03$, $p = 0.04$ respectively, Table II). Moreover, FEV and FEV₁%, reflecting airway obstruction, were also significantly reduced in study patients compared to healthy subjects ($p = 0.04$ and $p = 0.0002$; respectively, Table II).

Mean BNP level was higher in study patients than in the control group ($p = 0.00001$, Table II). No correlations were found between BNP concentrations and results of cardiopulmonary exercise tests, age of the patients at the time of CHD surgical correction or current age. In NYHA class I patients mean BNP level of 13.5 ± 8.6 pg/ml was significantly lower than 145.1 ± 86.3 pg/ml in NYHA class II patients ($p = 0.00001$), but similar to that in healthy controls (10.9 ± 8.2 pg/ml).

Discussion

Most study patients with a morphological RV serving the systemic circulation and those after Fontan operation were asymptomatic; only one third of them reported moderate exercise intolerance. The European Heart Survey, a large European registry including adult patients with congenital heart disease [19], reports similar results in patients with a morphological right ventricle serving the systemic circulation and worse exercise tolerance in patients with common ventricle physiology after Fontan operation, which is reduced in 60% of them. Better exercise capacity than in our study is reported occasionally in patients with atrial switch operated TGA and CCTGA [30]. However, long-term follow-up studies reveal that by the 4th decade of life over 50% of patients with CCTGA develop heart failure [1, 2], and 25-88.5% of patients 25 years after Senning/Mustard operation for TGA present severe heart failure symptoms [4, 5]. Our results are similar to those of Piran *et al.* [8], who reported symptoms of heart failure in 22% of atrial switch operated TGA patients, 32% of patients with CCTGA and 40% of patients after Fontan operation. Cardiopulmonary exercise test, providing objective assessment of exercise capacity, revealed its significant reduction in study patients. A discrepancy between favourable self-reported tolerance of exercise and reliable measures of exercise capacity resulting from long-term adaptation in such patients, similar to that observed in other types of congenital heart disease, has been reported previously by our team [16-18, 35], as well as by other investigators [15]. The main cause of

heart failure in study patients appears to be dysfunction of a morphological right ventricle serving the systemic circulation. Using contrast-enhanced magnetic resonance imaging Giardii *et al.* [24] documented structural and functional RV abnormalities in patients with CCTGA and atrial switch operated TGA subjects. They observed extensive fibrosis resulting most likely from inadequate perfusion of hypertrophic myocardium and probably also from insufficient myocardial protection during cardiac surgery in the past. These myocardial changes lead to reduced contractility of a morphological RV serving the systemic circulation. Patients with a common ventricle after Fontan operation have diminished cardiac output despite having only marginal ventricular dysfunction, which is mainly due to the absence of the pulmonary ventricle [9]. In patients with a morphological right ventricle or single ventricle serving the systemic circulation, atrioventricular valve incompetence increasing during exercise leads to significant volume overload of ventricles [2, 8, 9, 35]. Cardiac output in patients after Mustard/Senning operation for TGA and especially in patients after Fontan operation is highly dependent on preload. In the former situation it is mainly the result of low atrial buffalo compliance [4, 10]. In the latter one passive ventricular filling depends on venous pressure [7, 11].

Our study, consistently with results reported by other investigators [15, 23, 36, 37], confirmed the significant role of pulmonary dysfunction in the development of heart failure in adult patients with CHD. Patients in our study presented with spirometric abnormalities consistent with impaired pulmonary elasticity as well as airway obstruction resulting most likely from prior surgery with lung scarring, diaphragmatic palsy, atelectasis and cardiomegaly [15, 36, 37].

We have shown that in patients with a morphological right ventricle serving the systemic circulation and common ventricle physiology after Fontan operation maximal heart rate at peak exercise is reduced as compared to healthy adults. Similar observations in patients with CCTGA were made by Friedriksen *et al.* [37], and by Nozori *et al.* [26] in an unselected group of adult patients with congenital heart disease of whom many underwent Mustard/Senning operation for TGA. However, this was not confirmed by Canadian investigators [30]. According to Gillian *et al.* [6] lower heart rate at peak exercise in patients with TGA after atrial switch operation may represent an adaptive mechanism facilitating ventricular filling via noncompliant atrial buffalo. Similar observations suggesting clinical relevance of an impaired chronotropic response in adult heart failure patients with congenital heart disease have been reported

by others [15, 23, 26]. A team of investigators from Royal Brompton Hospital [37] has shown chronotropic incompetence to be a risk factor of death in such patients [38]. Finding that 15 patients (37.5% of the study group) failed to reach 80% maximum predicted age-adjusted heart rate at peak exercise, which is believed to worsen the prognosis, may reflect potential risks in our study population [38]. This rate is similar to that reported by Norozi *et al.* [26], who studied a group including patients with complex cyanotic heart disease and those with Fontan physiology, but still significantly higher than in patients with ischaemic heart disease (11%) or dilated cardiomyopathy (25%) [39].

Another diagnostic and prognostic factor in heart failure is B-type natriuretic peptide [1, 20, 21, 33]. We have found significantly increased serum concentrations of BNP in patients with a morphological RV serving the systemic circulation and in those after Fontan operation. Similar findings were reported by Laarsen *et al.* [40]. Higher BNP levels were also documented in patients with a right ventricle serving the systemic circulation in a population including many subjects with CCTGA, atrial switch operated TGA and after Fontan operation [29]. Limited reports on BNP levels in patients with common ventricle physiology after Fontan operation are inconsistent. Ohuhi *et al.* [14] found increased concentrations of BNP only in symptomatic patients, especially in subjects operated on using atrio-pulmonary connection, presenting with a markedly enlarged right atrium, where natriuretic peptide is produced. Of note, all patients after Fontan operation in our study were survivors of such procedures. Increased serum BNP levels in patients after Fontan operation were reported by Inai *et al.* [9]. Like us, they also did not find a significant correlation between BNP concentration and peak oxygen uptake during cardiopulmonary exercise testing. They also failed to provide evidence for a prognostic role of serum BNP level during 4-year follow-up. In contrast, Law *et al.* [27] did not find a significant increase of serum BNP levels in patients after Fontan operation who presented with clinical symptoms and haemodynamic evidence of heart failure. Such equivocal findings on BNP levels probably result from complex pathophysiology of heart failure in the studied patients. Although, as reported by others, BNP concentrations were higher in patients in more advanced NYHA functional classes [23, 29, 40], they did not correlate with results of cardiopulmonary exercise testing. BNP release has been documented to be mainly dependent upon myocardial wall stress resulting from pressure and volume overload [16-18, 21, 27-29, 30-34]. In study patients reduced preload, attenuating BNP production in the heart, is an additional factor

contributing to heart failure. According to the results of our study and previously published reports serum BNP level has no diagnostic value in patients with a right ventricle serving the systemic circulation or common ventricle physiology.

In conclusion, patients with a morphological right ventricle serving the systemic circulation and with common ventricle physiology after Fontana operation show markedly reduced exercise capacity. They are also characterized by higher serum concentrations of BNP, which do not however correlate with cardiopulmonary exercise test parameters.

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