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ORIGINAL ARTICLE

Exercise Capacity in Children and Adolescents with Corrected Congenital Heart Disease

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Abstract Congenital heart disease promotes hemodynamic changes that can contribute to reduce exercise capacity. The aim of the study was to evaluate the exercise capacity of children and adolescents with cyanotic congenital heart disease and to assess respiratory muscle strength, plasma levels of B-type natriuretic peptide and ventricular ejection fraction, as well the associations between these variables. Cross-sectional study that evaluated 48 patients between 6 and 18 years-old that underwent a six-minute walk test (6MWT), respiratory muscle strength, dosage of B-type natriuretic peptide and echocardiography. The mean age was 13.3 ± 4.1 years, and the most prevalent heart disease was tetralogy of Fallot (54.2 %). The average distance walked was 452.7 ± 73.2 m, significantly below the predicted (69 %) ($p < 0.001$). The maximum inspiratory pressure was above the predicted result (111.4 %), average 58.2 ± 22.3 ($p = 0.56$), and the maximum expiratory pressure was 63.2 ± 23.3 cm H_2O, significantly below the predicted (63 %) ($p < 0.001$). The level of B-type natriuretic peptide was elevated in all patients, with a median of 2087.17 (502.54–4,768.05). The ventricular ejection fraction showed a median of 65.9 (41–100). There was no correlation between the 6MWT, ventricular ejection fraction ($r = -0.05$; $p = 0.72$), inspiratory muscle strength ($r = 0.03$; $p = 0.81$), expiratory muscle strength ($r = 0.09$; $p = 0.05$) and B-type natriuretic peptide ($r = -0.04$; $p = 0.77$). Children and adolescents with cyanotic congenital heart disease present a lower exercise capacity and expiratory muscle strength. No associations were found between exercise capacity, respiratory muscle strength, B-type natriuretic peptide and left ventricular ejection fraction.

Keywords Six-minute walk test · Respiratory muscle strength · B-type natriuretic peptide · Ventricular ejection fraction

Academic link: This work is part of a master's thesis.

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Introduction

Surgical correction of congenital heart diseases (CHD) has contributed to a substantial increase in the survival rates of these patients, resulting in a quality of life close to normal. However, clinical signs of decompensation such as cyanosis, dyspnoea and nutritional changes [32], as well as reduced exercise capacity, may occur in patients, even after surgical correction of the disease [29].

The incidence of CHD in the USA can vary from 6 to 13 in 1,000 live births [19]. This variation is explained by the use of different diagnostic methods that facilitate the

detection of less severe heart diseases. Although less frequent, estimates in developing countries are around 8 in 1000 live births [30].

Congenital heart diseases are associated with organic abnormalities, both previously as after surgical correction of the defect. Among these, changes in nutritional status, height and weight as well as reduced exercise capacity are included [10]. The causes of reduced exercise capacity in CHD patients may be related to hemodynamic changes, to electrical conduction disturbances, ventricular pressure and volume overload, change in simpatovagal activity, increased neurohumoral activity [5], reduction in lung function [23] and changes in muscle metabolism [1].

The methods currently used to evaluate exercise capacity are the cardiopulmonary exercise test (CPET) and the six-minute walk test (6MWT), as a standardized measure of submaximal exercise capacity [2, 3]. The 6MWT has been considered a suitable replacement of the maximum effort test, since it is easily tolerated by patients with chronic diseases or in vulnerable populations. The test evaluates performance at submaximal level and thus seems to provide most appropriate information about the daily reality of patients, reflecting the degree of functionality during exercise. In addition, its easy and low-cost applicability makes the 6MWT a more available assessment option in the daily routine of reference centers, hospitals and clinics [14].

Few studies have been conducted with the 6MWT in children and adolescents with CHD, and the results show a reduced exercise capacity in these patients [24, 28, 36]. Effects of congenital heart disease on respiratory muscles can also contribute to the reduction in exercise capacity. Similar to what occurs in patients with heart failure, the metabolism of skeletal muscles, including the respiratory muscles, may be affected [1]. Chronic hypoxemia that results from CHD reduces the supply of oxygen to the muscles, generating early fatigue [1, 16].

The measurement of respiratory muscle strength through manovacuometry is used frequently in patients with chronic heart and lung diseases. However, the function of respiratory muscles is not assessed as often as needed in children and adolescents with heart disease so that the functional capacity of these patients is not adequately known [13, 40].

The level of serum B-type natriuretic peptide (BNP) is another important criterion of growing use in the assessment of prognosis, morbidity and mortality in patients with heart disease [12, 27]. The production of this neurohormone is increased in the presence of volume and pressure overload of the left ventricle, especially in cases of chronic heart failure in adults (HF) [20]. Although little is known about BNP levels in CHD, it is suggested that it may reflect changes in the functional capacity of patients, constituting therefore an important tool in the evaluation of this patient group [20, 39].

The recommendation for increased safe physical activity in this population of patients encourages attitudes that minimize risk and maximize the quality of life, which are very important in the management of patients and important tools for the normal development of the child [38]. However, in Brazil, there is still little information on the exercise capacity in CHD patients. The adequate follow-up of these patients through a complete functional assessment allows health professionals to determine the need for referral to cardiac rehabilitation programs or sports activities, without the risk of negative outcomes [31, 4].

Therefore, the objective of this study was to evaluate the exercise capacity of children and adolescents with corrected cyanotic CHD. Secondary objectives included assessment of the respiratory muscle strength, plasma levels of BNP and heart function, as well as the possible association between these variables.

Materials and Methods

Study Design

This analytical cross-sectional study was conducted through convenience sample.

Sample

The sample was composed by children and adolescents between 6 and 18 years of age, with a diagnosis of cyanotic CHD and who had already undergone surgery for correction of heart diseases. The patients were in clinical follow-up at the outpatient Pediatric Cardiology Institute of Cardiology/Fundação Universitária de Cardiolodia de Porto Alegre/Brazil.

Subjects

Forty-eight children and teenagers between 6 and 18 years of age with a diagnosis of cyanotic CHD were included in the study. All patients underwent previous surgery to correct the heart defect. Patients with acute febrile or general malaise and those with orthopedic, trauma or neurological conditions that could influence the tests were excluded from the study. Parents and/or caregivers signed a post-informed consent. This study was approved by the Research Ethics Committees of Universidade Federal de Ciências da Saúde de Porto Alegre—UFCSPA—under number 12/041, and of Institute of Cardiology/Fundação Universitária de Cardiolodia under number 4634/11. The tests were conducted at Institute of Cardiology/Fundação Universitária de Cardiologia de Porto Alegre, Rio Grande do Sul, Brazil.

Variables and Instruments

Personal and sociodemographic data, in addition to information related to the baseline disease, were collected. The following clinical variables were collected at rest: heart rate, peripheral oxygen saturation by pulse oximetry (*New Tech PM 100C*®), respiratory rate by observing the respiratory movements during 1 min, blood pressure using a sphygmomanometer (*G-Tech*®), weight and height using a scale and a stadiometer(*Welmy*®).

Body Mass Index

Patients were classified as eutrophic, low weight/undernourished or overweight/obese based on the curve of body mass index (BMI) in relation to age and sex of children/adolescents between 2 and 20 years of age, proposed by the National Center for Health Statistics (NCHS) [21]. Eutrophic status was considered when BMI was between the 25th and 75th percentile, low weight/undernourished when the BMI was <25th percentile, and overweight/obese when the BMI was >85th percentile.

Respiratory Muscle Strength

Respiratory muscle strength was assessed using a digital manovacuometer (*Globalmed*® MVD300), which included an oral nasal clip and one-way valve. The maximum expiratory pressure (MEP) was determined from the total lung capacity (TLC), measured with the individual in a sitting position and properly positioned. The maximum inspiratory pressure (MIP) was determined from the residual volume, measured with an intense stimulus for individuals to achieve the maximum effort. All guidelines relative to the reproducibility and acceptability of the maneuvers were followed. The test was conducted following the recommendations from the American Thoracic Society (ATS)/European Respiratory Society (ERS) [4]. The equation proposed by Wilson and collaborators [42] was used for comparison between the results obtained with patients and the predicted value.

The Six-Minute Walk Test (6MWT)

The 6MWT was performed according to the standards proposed by the American Thoracic Society (ATS) [2], with only one repetition. The subjects were instructed to walk as much as possible along a 30-m long corridor, marked at every three meters, with interruption or slowing down the rhythm if necessary. Standardized phrases of encouragement were played every minute of the journey: *"You're doing great. You have 5 min". "Keep going, good work. You have 4 min". "You're doing great. You're halfway there". "Keep up the good work. There are only 2 min left". "You are doing well. There's only 1 min left"*. At the end of the test, the total distance travelled was measured. The heart rate, peripheral oxygen saturation, blood pressure and respiratory rate were evaluated at the beginning and end of the test, as the modified BORG scale, used to assess the subjective sensation of dyspnea and fatigue of the lower limbs. The equation described by Geiger and collaborators [15] was used to compare the results with predicted values.

Dosage of Plasma B-type Natriuretic Peptide (BNP)

To prevent early fatigue or changes in heart rate, respiratory rate and blood pressure, patients were conducted in a wheelchair to the Clinical Analysis Laboratory of Institute of Cardiology, Fundação Universitária de Cardiologia, for blood collection. With the patient in a sitting position, a 4-ml sample of blood was drawn from an antecubital vein and placed in a tube with EDTA (*Vacuplast*®*-Collect Line*). Immediately after collection, the blood samples were centrifuged (*Eppendorf*® *Centrifuge 5804R 15 amp version*) at 1,000 rpm for 10 min, at 4 °C. The plasma was then removed from the bottle with a P1000 pipette (Gibson® CE) and stored at −20 °C. BNP levels were determined by a biomedical professional responsible for the laboratory, using an ELISA kit (*Biomedica Slovakia s.r.o.*).

Transthoracic Echocardiography

Echocardiography exams were performed at the Pediatric Echocardiography Service of IC-FUC, as a routine procedure of the Pediatric Cardiology Outpatient Clinic. All patients underwent transthoracic echocardiography through conventional evaluation, at rest. Final systolic and diastolic diameters were measured through the internal dimensions of the left ventricular cavity obtained by two-dimensional imaging and M-mode in the longitudinal parasternal view. The left ventricular ejection fraction was estimated by the Teichholz formula, in accordance with the recommendations of the European Society of Echocardiography and the American Society of Echocardiography [22]. The left ventricular mass was calculated by the Devereux formula and then indexed by body surface area. The echocardiography was not performed in seven patients, totaling thus 41 subjects with complete echocardiogram reports.

Statistical Analysis

The Shapiro–Wilk test was initially used to assess the normality of the data. Continuous data with parametric distribution were expressed as mean and standard deviation, and nonparametric data as median, minimum and maximum. The qualitative variables were expressed as absolute and relative frequency. The Student's *t* test for

paired samples was used for comparison between the values obtained and predicted. The existence of associations was assessed with the Spearman correlation test. The significance level was set at 5 % ($p \leq 0.05$). All analyses were conducted with the program *Statistical Package for the Social Sciences*—SPSS version 17.

Sample Size

The sample size was calculated with the aid of the software *Pepi* version 4.0. According to a previous study by Moalla et al. [24], the standard deviation of the distance walked in the 6MWT in the CHD group was 17.1 m. Accepting a maximum error of 5 m in the estimate, a significance level of 5 % ($p \leq 0.05$) and power of 0.80, the estimated sample size was of 48 patients.

Results

General Characteristics

Forty-eight subjects participated in the study. Thirty (62.5 %) were male, most of them (22, 45.8 %) were from the interior of the State of Rio Grande do Sul, and 18 (37.5 %) were from the metropolitan region. Only eight patients (16.7 %) came from the capital city.

Thirty-six patients (75 %) did not use any kind of medication and 12 (25 %) used diuretics, beta-blockers, anticoagulants and angiotensin-converting enzyme inhibitors, sometimes in association. All patients had undergone palliative surgery with total correction of the defect until the first year of life. Other characteristics of the sample are presented in Table 1. The prevalence of heart defects was tetralogy of Fallot (54.2 %) and transposition of the great vessels (16.7 %), followed by other pathologies. The BMI classification proposed by NCHS [21] is shown in Table 1. All patients in the study reported not to perform regular physical activity.

Respiratory Muscle Strength

With respect to respiratory muscle strength, the average maximum inspiratory pressure was higher than predicted for age and gender, with a tendency to significance. By contrast, the average maximum expiratory pressure was significantly lower than the predicted values (Table 2).

There was no correlation between the distance walked in the 6MWT, the maximum expiratory pressure ($r = 0.09$; $p = 0.05$) and the maximum inspiratory pressure ($r = 0.03$; $p = 0.81$) (Table 3).

In a subgroup analysis, patients were divided into two groups consisting of absent/mild residual lesion ($n = 31$) and moderate/severe residual lesion ($n = 10$. Of these, 4 had moderate and 6 had severe residual lesions). The group with moderate-to-severe residual lesion presented the lower values of MEP, i.e., a worse performance related to the greater severity of the residual lesion, but with no statistical significance ($p = 0{,}057$).

Table 1 Baseline characteristics of patients

Variables	$n = 48$
Age (years)[a]	13.3 ± 4.1
Male sex *n* (%)	30 (62.5 %)
Weight (kg)[a]	51.0 ± 21.3
Height (m)[a]	1.51 ± 0.19
BNP (pg/dl)[b]	2087.17 (502.54–4768.05)
BMI (Kg/cm^2)[a]	21.4 ± 6.4
BMI—thinness	6 (12.5 %)
BMI normal	24 (50.0 %)
BMI overweight	14 (29.2 %)
BMI obesity	4 (8.3 %)
Ejection fraction (%)[b]	65.90 (41–100)
Fractional shortening (%)[b]	37.76 (20–100)
LVESV (ml)[b]	21.49 (4–54)
LVEDV (ml)[b]	59.33 (30–92)
Ventricular stroke volume (ml)[b]	37.95 (17–85)
Drugs in use	12 (25.0 %)

Data are presented as mean ± SD or *n* (%)

BNP brain natriuretic peptide, *BMI* body mass index, *LVESV* left ventricular end-systolic volume, *LVEDV* left ventricular end-diastolic volume

[a] Mean and standard deviation

[b] Median (minimum − maximum)

Six-Minute Walk Test

All study subjects completed the 6MWT without interruption. One patient presented peripheral cyanosis and referred a moderate dyspnea. All patients reported some degree of fatigue, especially in the lower limbs, during walking, and 50 % reported a fatigue level between one and five on the BORG scale. The average heart rate at rest was 77.71 (43–126) and 100.81 (49–149) after the 6MWT. The peripheral oxygen saturation was in average 97.29 (80–99) at rest and 95.35 (74–99) after the 6MWT. The average distance walked by the participants was significantly lower than the predicted values (Table 2).

The distance walked in the 6MWT showed no significant correlation with any of the variables studied (Table 3).

B-type Natriuretic Peptide

All patients showed increased plasma levels of BNP. Table 1 shows the median and the minimum and maximum

Table 2 Comparison between predicted and measured values of the distance walked in 6MWT and respiratory muscle strength

Variables	Obtained	Predict	% of predict	*p* value
MIP (cmH_2O)	−58.2 ± 22.3	−52.1 ± 4.4	−111.4 ± 40.0	0.056
MEP (cmH_2O)	63.2 ± 23.3	101.9 ± 23.4*	63.0 ± 21.5	<0.001
Distance 6MWT (m)	452.7 ± 73.2	656.9 ± 52.1*	69.0 ± 10.4	<0.001

Data are presented as mean ± SD Student's *t* test (Paired Samples)

MIP maximal inspiratory pressure, *MEP* maximal expiratory pressure, *6MWT* 6-minute walk test

* Statistical significance between values obtained and predicted

Table 3 Correlations between functional capacity (6MWT) and respiratory muscle strength, ejection fraction, BNP and BMI

Variables	6MWT	
	Correlation coefficient ρ	*p* value
MIP	0.03	0.81
MEP	0.09	0.04
Ejection fraction	−0.05	0.72
BNP	−0.04	0.77
BMI	0.01	0.34

ρ Spearman correlation coefficient

MIP maximal inspiratory pressure, *MEP* maximal expiratory pressure, *BNP* brain natriuretic peptide, *BMC* body mass index

* Statistical significance $p < 0.05$

values of plasma BNP. No correlations between BNP and distance walked, expiratory muscle strength ($r = -0.04$ $p = 0.75$) or ventricular ejection fraction ($r = -0.01$ $p = 0.47$) were observed (Table 3).

Echocardiography

Echocardiographic variables evaluated in this study included the left ventricular ejection fraction, the fractional shortening (delta D), end-systolic and diastolic volume and stroke volume. Four patients (9.75 %) presented left ventricular ejection fraction between 40 and 50 %, 9 (21.9 %) between 50 and 60 %, 16 (39 %) between 60 and 70 % and 12 (29.3 %) above 70 %. The median and the minimum and maximum values of these variables are presented in Table 1.

Thirty-one patients (64.6 %) were classified in the subgroup absent/light residual lesion, and 10 (35.4 %) represented the subgroup of moderate-to-severe residual lesion. According to the echocardiographic diagnosis, the residual lesions with higher prevalence were aortic stenosis, pulmonary valve insufficiency and ventricular septal defect.

Discussion

The main objective of this study was to evaluate the submaximal exercise capacity in children and adolescents with corrected cyanotic CHD and, as secondary aims, to assess the respiratory muscle strength, plasma levels of BNP and cardiac function, as well as the possible association between these variables.

The general mechanisms involved in reducing the exercise capacity in patients with CHD are multifactorial. Different aspects may contribute to maintain this condition, including insufficient knowledge of the family and educators about the disease [26], low perception of the patient's health situation [6] and the anxiety of the family, with a possible association existing among them [25].

The results of the present study confirmed the reduced exercise capacity previously reported by Moalla et al. [24]. The study evaluated 17 children with congenital heart disease by the 6MWT, showing walked distance values significantly lower for the patients than for healthy controls ($p < 0.001$). In a similar study, Sen et al. [34] compared, using the 6MWT, the submaximal exercise capacity in children after Fontan and Glenn surgery. The results showed that the performance of patients submitted to Fontan surgery was significantly lower compared to that submitted to the Glenn procedure, demonstrating that this submaximal test was able to differentiate between more and less severe conditions. The study also concluded that factors such as surgery at an early age, lower resting heart rate and higher resting peripheral oxygen saturation were associated with better 6MWT performance.

Carvalho et al. [8] described a direct relation between the degree of pulmonary regurgitation and reduced exercise tolerance. The maximal effort test showed a significantly lower total time of exercise duration and maximal oxygen consumption in patients aged between 7 and 12 after surgery for correction of tetralogy of Fallot, compared with healthy controls. Other studies suggest that exercise intolerance may result from factors such as low pulmonary blood flow with inadequate oxygenation [37], reduction in cardiac output due to increased pulmonary vascular resistance [33], and impairment of skeletal musculature, possibly caused by reduced muscle blood flow during exercise [18].

In addition to the aforementioned causes, we hypothesized that the reduced exercise capacity of patients in

the present study, represented by the shorter distance walked, may be associated with a sedentary lifestyle. All patients reported not practicing any type of physical activity at school or at home.

Patients in the present study showed a reduction in respiratory muscle strength, with a significantly lower maximum expiratory pressure than the predicted values in healthy children. The maximum inspiratory pressure was different than expected, with results above the predicted value.

We believe that the expiratory pressure reduction is related to the impairment of left ventricular ejection fraction (LVEF) and consequently to low cardiac debit, since 71 % of our patients had a LVEF below 70 %. The low oxygen supply to muscles during exercise, usual in cases of chronic hypoxemia, can also affect muscle strength. Some of our patients presented resting peripheral oxygen saturation lower than 90 %. In addition, after the completion of 6MWT, more than half of the patients presented saturation lower than 90 %.

The results of this study confirm the observations of Greutmann [16], who compared the peripheral and respiratory muscle strength of 51 young adults with diagnosis of cyanotic CHD and healthy controls. The expiratory pressure was 70 % below the predicted values in cardiac patients and significantly lower than in controls (85 ± 32 vs. 116 ± 415, respectively).

Adatia et al. [1] described skeletal muscle abnormalities in children and adolescents with cyanotic CHD during sleep, exercise and muscle recovery. The study was conducted with patients performing plantar flexion exercise while an image was captured through phosphorus magnetic resonance spectroscopy. The results showed abnormalities in the synthesis of adenosine triphosphate (ATP) due to limited muscle oxygen supply, which is usual in cases of chronic hypoxemia and is frequently found in cyanotic heart diseases.

BNP values are typically high in clinical situations of pressure and volume overload, as in cases of heart failure [11], as well as in children with congenital heart disease [9, 41]. An increase in plasma BNP level was observed in all patients in the present study, even in the absence of a diagnosis of HF or pulmonary arterial hypertension (PAH). However, we found no association of BNP values with submaximal exercise capacity assessed by the 6MWT. This was possibly due to fact that the exercise capacity was assessed through a submaximal test.

BNP levels were reported to be significantly higher in 32 patients aged 14.7 ± 3.1 years, submitted to repair of tetralogy of Fallot, than in 20 healthy adolescents ($p = 0.027$), and correlated negatively with the duration of exercise ($r = -0.45$, $p = 0.021$) and oxygen consumption at peak exercise ($r = -0.43$, $p = 0.03$) [9]. The authors concluded that the BNP correlated with right ventricular volume overload and lower exercise capacity in these patients.

Echocardiographic results showed that most patients in this study presented LVEF lower than 70 % and that more than one-third of them had stenosis and pulmonary valve insufficiency and ventricular septal defect classified as moderate-to-severe residual lesions. However, no associations were observed between cardiac function and exercise capacity or respiratory muscle strength. We hypothesized that this lack of association may be due to the use of a submaximal test, which does not generate greater overload on cardiac function (ventricular ejection fraction) and, consequently, on the cardiac output [35]. All the changes observed by echocardiography, however, have a significant hemodynamic impact, raising the long-term mortality risk or decreasing exercise performance [7, 17], which may explain partially the reduction in exercise capacity and the lower expiratory muscle strength observed in patients in the present study.

This study has some limitations such as the presence of different cyanotic CHD, which were not stratified by specific type and severity, as well as by physical limitations. In addition, the physical activity level of patients was not quantitatively evaluated, due to the difficulty of preschool children to interpret the questionnaires.

Conclusion

In conclusion, this study showed that children and adolescents with cyanotic CHD, even after surgical repair, present low submaximal exercise capacity and low maximum expiratory muscle strength. The plasma level of BNP was elevated in all subjects.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest I declare that there is no conflict of interest.

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