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Comparison of the Degree of Exercise Tolerance in Children After Surgical Treatment of Complex Cardiac Defects, Assessed Using Ergospirometry and the Level of Brain Natriuretic Peptide

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Abstract: Children who underwent surgery for complex congenital heart defects present worse exercise capacity than their healthy peers. In adults and adolescents, heart failure is assessed on the basis of clinical symptoms using the New York Heart Association (NYHA) score, while in an infant Ross scale; heart failure can also be evaluated by other parameters. The purpose of this study was to compare the degree of exercise tolerance in children after surgery for complex heart defects, assessed by the ratio of maximum oxygen uptake (VO2max) and the brain natriuretic peptide (N-terminal fragment of the prohormone brain-type natriuretic peptide [NT-proBNP]) concentration.

The study group consisted of 42 children, ages 9 to 17 years (mean 14.00 ± 2.72). Among them there were 22 children with tetralogy of Fallot (ToF) after total correction, 18 children with transposition of the great arteries (d-TGA) after the arterial switch operation, and 2 children with single ventricle (SV) after the Fontan operation. All but 1 child were in NYHA class I. The control group consisted of 20 healthy children. Outcomes of interest were the ratio of VO2max, determined during ergospirometry, and the level of NT-proBNP. The statistical analysis was performed and the groups were considered significantly different for $P < 0.05$.

There was no statistically significant correlation between NT-proBNP and maximum oxygen uptake (VO2) kg^{-1} min^{-1} in the study group compared with the control group.

The VO2max in the test group had a mean value less (34.6 ± 8.0) than controls (38.4 ± 7.7), and the differences were statistically significant ($P = 0.041$). In contrast, the average concentration of NT-proBNP in the study group was higher than controls (117.9 ± 74.3 vs 18.0 ± 24.5), and these differences were statistically significant ($P < 0.001$).

After operations for complex heart defects (ToF, TGA, and SV), children have worse heart function parameters and exercise capacity than the healthy population. To control this, we recommend postoperative ergospirometry and determination of NT-proBNP concentrations.

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Abbreviations: ANP = atrial natriuretic peptide, d-TGA = transposition of the great arteries, ECG = electrocardiography, Holter ECG = 24-h electrocardiographic Holter monitoring, NT-proBNP = N-terminal fragment of the prohormone brain-type natriuretic peptide, NYHA = New York Heart Association, peak VO2 = peak oxygen uptake (during maximal exercise), RAAS = renin–angiotensin–aldosterone system, RER = respiratory exchange ratio, RVOT = right ventricle outflow tract, SV = single ventricle, ToF = tetralogy of Fallot, VO2max = maximum oxygen uptake.

INTRODUCTION

In children, after operations to treat complex congenital heart defects, such as tetralogy of Fallot (ToF), transposition of great arteries (TGA), and single ventricle (SV), there are numerous residual changes and cardiac dysrhythmias that significantly affect exercise capacity.

ToF is a complex cyanotic congenital heart defect that consists of a defect in the intraventricular septum, stenosis in the right ventricular outflow tract, dextroposition of the aortic root, and right ventricular hypertrophy. ToF is approximately 3.5% of all heart defects and was 1 of the first complex congenital heart defects to be corrected surgically.

The effects of surgery at the present time are good. It is believed that at least 90% of patients survive 30 years or more; however, due to the complexity of the anomalies, the early and late postoperative period may occur with residual changes of different intensity.[1–3] The most common include systolic gradient through the right ventricle outflow tract (RVOT), residual ventricular septal defects, and pulmonary valve insufficiency; these quite often include ventricular arrhythmias and conduction disturbances, especially complete block of the right bundle branch.[4,5]

Another anomaly, TGA, is treated by the Jatene (arterial switch) operation, which restores proper hemodynamic conditions. In TGA, after the surgery for residual stenosis at the junction of the aorta and pulmonary trunk, coronary artery stenosis, widening pad ''neoaorty,'' and aortic valve insufficiency may also occur. Enlargement and left ventricular dysfunction is also described as a consequence of abnormal myocardial perfusion in the transplanted coronary arteries.[6]

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However, in children with SV, the Fontan operation is performed. The aim of the operation is the connection of the superior and inferior vena cava to the pulmonary artery; unfortunately, this type of operation is burdened with a number of complications that affect the child's condition and subsequent exercise capacity.[7–9]

Recently, the results of treatment in children with those complex heart defects are getting better and better; it is expected that these children should lead normal lives, go to school, and be able to participate in physical activities. Therefore, it is necessary, in addition to carrying out standard checks (laboratory tests, standard electrocardiography [ECG], Holter ECG, echocardiography, etc.) to evaluate their physical capacity. The aim of this study was to plan a specific range of physical activities appropriate to the current possibilities of these patients.

Simple tests to assess the condition of the cardiovascular system and its capacity are still required. The factors that play important roles in cardiovascular diseases are the natriuretic peptides, which have been used in the diagnosis of heart failure. It has been demonstrated that brain natriuretic peptide (BNP) and its N-terminal portion (NT-proBNP) are sensitive and useful indicators of impaired systolic and diastolic function.[10–12] Another method of evaluating the efficiency of patients after heart surgery may be the more widely used ergospirometry, which connects a classic stress test with measurements of exhaled gases in the air.

The absorption coefficient of oxygen (VO2) is considered a reliable and valuable parameter for evaluating exercise capacity. Performance of the ergospirometry test is possible only with children at least 7 to 8 years of age, because the child must collaborate with the technician during the test; the use of facial masks is also a significant discomfort.[13,14]

In contrast, assaying NT-proBNP is easy and only requires taking a small blood sample for analysis.

The purpose of this study was to compare the degree of exercise tolerance in children after surgery for complex heart defects, as assessed by the ratio of maximum oxygen uptake (VO2max) and NT-proBNP concentration.

METHODS

The study group consisted of 42 children, ages 9 to 17 years (mean 14.00 ± 2.72). Among them there were 22 children with ToF after total correction, 18 children with TGA after the arterial switch operation, and 2 children with SV after the Fontan operation. All but 1 child were in New York Heart Association (NYHA) class I.

The control group consisted of 20 healthy children ages from 7 to 17 years (mean 14.90 ± 2.48). During examination, the patients underwent laboratory tests, ECG, 24-h Holter ECG, echocardiography, and chest X-ray.

Inclusion criteria include kind of heart defects and operations, written consent signed by the parents and the patient when he or she was at least 16 years old, and cooperation during the investigation. Exclusion criteria include severe residual changes (protein loss syndrome, fluid in the abdomen, cardiac arrhythmia, metabolic disorders, hypoxic brain damage) impeding the implementation study of ergospirometry test, as well as lack of consent, and a lack of patient cooperation.

Ergospirometry, in all participants, was performed using a treadmill (nSpire Health GmbH, Schlimpfhofer Straße 14, D-97723 Oberthulba, Germany) and the RAMP protocol.

The primary parameter we evaluated was the proportion of oxygen uptake, VO2 kg^{-1} min^{-1}, which was determined after obtaining a respiratory exchange ratio (RER) >1.0 (so-called exceeding the anaerobic threshold) or during maximal exercise (peak VO2).

Exercise capacity was evaluated by comparing our own results with standards from the literature. The levels of NT-proBNP in the study and control groups were indicated using reagents from Biomedica Medizine Producte, Austria, Vienna.

The research protocol was approved by the Bioethical Commission of the Silesian University of Medicine and therefore was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The results were statistically analyzed by Statcenter Company. Calculations were performed using Statistica 10.

Initially, the distribution of normality was verified by a test of normality (Shapiro–Wilk).

Because distributions differed significantly from normality, we used nonparametric tests to test the significance of differences and correlations.

To compare 3 groups, the Kruskal–Wallis test was used, while the Mann–Whitney test was used to compare 2 independent groups.

The correlations between variables were tested with Spearman rank correlation coefficient.

All $P < 0.05$ were considered statistically significant.

RESULTS

The VO2/kg/min in the study group had a mean value less (34.6 ± 8.0) than controls (38.4 ± 7.7), and the differences were statistically significant ($P = 0.041$).

In contrast, the average concentration of NT-proBNP in the study group was elevated (74.3 ± 117.9) compared with the control group (18.0 ± 24.5); these differences were statistically significant ($P < 0.001$; Table 1).

Using a multiple comparison test, the analysis of the VO2 kg^{-1} min^{-1} and NT-proBNP was made within the study group.

There was no statistically significant difference in the VO2 kg^{-1} min^{-1} between the ToF, TGA, and SV groups ($P = 0.139$). The average VO2 kg^{-1} min^{-1} values in the ToF and TGA groups were similar: 34.5 and 36.9 mL kg^{-1} min^{-1}, respectively. The average VO2 kg^{-1} min^{-1} for the Fontan group was 26.0 mL kg^{-1} min^{-1}.

The NT-proBNP concentrations in the TGA and ToF groups were not statistically significantly different from each other (P = NS). Only the Fontan group had higher values than the TGA group; the difference was statistically significant ($P = 0.037$), but the size of this group was too small to be conclusive (Table 2).

There was no statistically significant correlation between NT-proBNP and VO2 kg^{-1} min^{-1} in the study group compared with the control group (Table 3).

We observed that the level VO2 kg^{-1} min^{-1} did not significantly decrease with increasing NT-proBNP in either the study group ($r = -0.044$) or the control group ($r = -0.069$).

DISCUSSION

In children, residual changes and arrhythmias may occur after operations to treat complex congenital heart defects. These changes significantly impact exercise capacity, understood as the ability to perform heavy or long-lasting physical exercises without rapidly increasing fatigue and internal environment changes.

Progress in medical care, cardiology, and cardiac surgery techniques has contributed to a significant increase in the survival of children with congenital heart defects.

TABLE 1. Maximum Oxygen Uptake (VO2max) and Brain Natriuretic Peptide (NT-proBNP) Concentration in the Study Group Comparing to Controls

	Group	N	Mean	Me	Min	Max	SD	P^*
VO2 kg^{-1} min^{-1}, mL kg^{-1} min^{-1}	Study	42	34.6	34.2	21.6	64.0	8.0	0.041
	Control	20	38.4	36.5	29.3	62.6	7.7	
NT-proBNP	Study	42	74.3	44.5	10.8	754.7	117.9	<0.001
	Control	20	18.0	9.6	5.2	115.9	24.5	

Max = maximum, Me = medina, Min = minimum, N = group size, NT-proBNP = brain natriuretic peptide, SD = standard deviation, VO2max = maximum oxygen uptake.
* The difference is significant at P value < 0.05.

Therefore, it is expected that the condition of these patients will be getting better and better and that they will lead normal lives, with physical activity appropriate to their capabilities.

Undoubtedly, the impact on exercise capacity stems from heart defects as well as postoperative complications.

It is therefore legitimate to look for simple tests to assess the status of the cardiovascular system and its efficiency in this group of children.

One of the basic parameters for assessing exercise capacity during ergospirometry is oxygen uptake by the body; that is, VO2.

If VO2 is determined during exercise, the maximum, then, is called the ratio of VO2max when the metabolically equivalent RER exceeds 1.05.

The anaerobic threshold point is when aerobic metabolism becomes anaerobic. Patients with heart failure often do not achieve the maximum effort from fatigue and, therefore, are not evaluated at their peak VO2. Both parameters are considered measures of physical fitness. VO2 is determined at the time of growing effort on a treadmill.

VO2 increases with increased effort until it reaches the maximum (plateau); further enhancement of the effort no longer increases its level.[13,14] VO2 is an indicator that can be measured in children that cooperate during the test (at least 7–8 years of age). Measuring VO2 provides objective information about the patient's clinical condition and the factors limiting exercise tolerance. Exercise intolerance is the primary symptom of heart failure. Ergospirometry studies are performed most often with patients with chronic heart failure. Weber et al[15] formed a 5-step aerobics classification of heart failure patients, according to which a mild insufficiency or lack of it occurs at peak VO2 values above 20 mL kg^{-1} min^{-1}; very heavy insufficiency was indicated by VO2 kg^{-1} min^{-1} values under 6.

TABLE 3. Correlation Between NT-proBNP and VO2 kg^{-1} min^{-1}

Spearman Rank Correlation Coefficient	N	R	P
NT-proBNP control group and VO2 kg^{-1} min^{-1} control group	20	−0.069	0.772
NT-proBNP study group and VO2 kg^{-1} min^{-1} study group	42	−0.044	0.782

N = the number of subjects, NT-proBNP = brain natriuretic peptide, P = the statistical significance, R = the Spearman rank correlation coefficient, VO2 = maximum oxygen uptake.

The value of 10 to 14 mL kg^{-1} min^{-1} is considered the threshold value, below which the patient should be eligible for heart transplantation.[16] Ergospirometry is performed to evaluate heart function before qualifying for certain surgical procedures and to evaluate the effectiveness of rehabilitation. It is also a recognized test for the assessment of physical fitness and the cardiovascular status of patients after operations to treat complex heart defects.[16–18] Currently, it is believed that ergospirometry and VO2 are likely to give the most accurate insight into the capacity of the patient and allow 1 to differentiate cardiac and pulmonary causes of exercise intolerance.

Heart failure can occur in both the early and the late postoperative periods. The neurohormonal activation system plays an important role in heart failure; the compensation of the circulatory system plays an important role in the elution of

TABLE 2. Multiple Comparison Test in the Study Group (ToF, TGA, and SV)

Study Group	Recognition	N	Mean	Med	Min	Max	SD
VO2 kg^{-1} min^{-1}, mL kg^{-1} min^{-1}	ToF	22	34.5	34.5	22.9	47.2	5.6
	d-TGA	18	36.9	34.3	21.6	64.0	10.5
	Fontana	2	26.0	26.0	23.6	28.3	3.3
NT-proBNP	ToF	22	57.1	55.3	14.3	112.2	29.1
	d-TGA	18	40.5	32.4	15.7	127.9	26.9
	SV	2	108.6	108.6	106.5	110.7	2.9

Max = maximum, Me = medina, Min = minimum, N = group size, NT-proBNP = brain natriuretic peptide, SD = standard deviation, SV = single ventricle, TGA = transposition of the great arteries, ToF = tetralogy of Fallot, VO2 = maximum oxygen uptake.

natriuretic peptides during the extension of the atria (atrial natriuretic peptide) and the chambers (BNP). These neurohormones have a natriuretic effect, dilate blood vessels, reduce adrenergic activity, directly inhibit the release of renin, and indirectly inhibit the release of angiotensin II and aldosterone.

Activation of natriuretic peptides in cardiac insufficiency occurs quickly, concurrent with the activation of the adrenergic system and ahead of the renin–angiotensin–aldosterone system, even before the symptoms of ventricular dysfunction. The elevated levels are present even in asymptomatic heart failure with reduced systolic and diastolic function. It has long been known that BNP level is considered an independent marker of adverse cardiac events and the concentration is raised during failure in the left or right ventricle. For these reasons, it is used in the assessment of cardiovascular capacity.[19–22]

In our work, cardiovascular fitness was assessed in children after surgery to treat complex congenital heart defects, based on VO2 and NT-proBNP.

We found that the VO2 levels in the study group were significantly lower than in the control group, suggesting that cardiovascular parameters were worse in children after the surgery to treat their heart defects. Furthermore, we have shown that children had higher NT-proBNP levels after the Fontan operation (108.6 pg mL^{-1}) than after surgery for FoT (57.1 pg mL^{-1}) or TGA (40.5 pg mL^{-1}).

In the literature, there are reports that NT-proBNP levels above 100 pg mL^{-1} indicate a high probability of heart failure. In our study, the lowest levels of NT-proBNP were found after the operation for TGA, which would be consistent with the low residual severity of postsurgery complications in that group.

Analyzing the VO2 values within the group (ToF, TGA, and SV), there were no statistically significant differences, although SV children had the worst average score (26.0 mL kg^{-1} min^{-1}), after providing for benign disorders of oxygen changes.

Unfortunately, the SV group was too small in our study, but the results are largely consistent with the literature. Fernandes et al conducted several ergospirometric studies in 1 group of 78 patients (age 19.7 ± 10.2 years) after Fontan operations; most of their subjects reached VO2 values similar to the results of our study (approx. 26 mL kg^{-1} min^{-1}, i.e., approx. 65% of the norm). Repeating the ergospirometric study, they found that, in patients after the Fontan operation, there is progressive worsening over time of the VO2, with the greatest reduction before age 18 (approx. 1.25% per year). After the age of 18, the VO2 decrease slightly declined, to approx. 0.54% per year.[7] The reduced exercise capacity due to Fontan surgery was also recorded in other reports.[17]

Marcuccio et al, similar to our work, found worse VO2 values in patients after surgery for ToF or complex congenital heart defects, respectively, than in healthy children.[23] Patients, after surgery for ToF, demonstrated results at 74% of normal, after surgery for TGA, 64% of the norm, and after surgery for SV, only 55% of normal. Lower values of VO2 after the operation for ToF were also observed in other reports.[24,25]

The VO2 was also evaluated in TGA children after arterial switch operations; they performed worse than healthy children.[6,18]

We observed BNP levels in our study that were higher in patients after surgery for complex congenital heart defects than in healthy children.

Cantinotti et al[12] found that higher BNP levels corresponded to the severity of residual lesions after surgery. Elevated levels of BNP after surgery for ToF, TGA, or SV were observed in other reports, suggesting that BNP can be used to predict ventricular systolic dysfunction. Cetin et al[26] had found, in a group of 25 patients after surgery for ToF (mean age 14.1 years), that VO2 was worse in the patients than the control group, and the patients had significantly higher concentrations of BNP.

Similar results were obtained by Cheung et al[27]; they suggested that the concentration of BNP depends on the right ventricular volume overload and pulmonary insufficiency. The available scientific papers predominantly analyzed adults; studies in children were less numerous.

Obtaining worse outcomes, and therefore lower VO2 values and higher BNP values, is probably due to the severity of postoperative residual masses. The efficiency of the right ventricle after the operation for ToF is the result of preoperative hypoxia and hypertrophy and of residual masses. Additionally, the so-called restriction physiology of the right ventricle has been described, where 1 can observe diastolic blood flow from the pulmonary artery to the pulmonary vasculature during atrial contraction, resulting in improved performance of the right ventricle, reducing its dilatation and arrhythmia severity, and shortening the duration of the QRS complex.[2] Occurring after the operation for ToF, right ventricular dysfunction and its volume overload depend on, among other factors, the RVOT gradient and duration of the operation.[26] In the literature, the correlation between BNP levels and the load volume of the right ventricle is confirmed.[11,26,27]

Narrowing of the outflow tract of the right ventricle and the increasing gradient are well tolerated for a long time, and many patients, despite even the advanced changes, are asymptomatic. After surgery, ToF patients suffer increased rates of hemodynamic changes in the heart and sudden incidents of adverse cardiac events, including sudden cardiac death. Based on many studies, the risk factors of sudden death in these patients include abnormal coronary arteries in the mouth, complex ventricular arrhythmias, and evident severity during exercise testing.

In adults, the duration of the QRS complex (especially over 180 ms) can coexist with sustained ventricular tachycardia and risk of sudden cardiac death. The elongation of the duration of the QRS complex often coexists with pulmonary valve regurgitation and right ventricular enlargement.[28] So, over time, the ToF operation increases the risk of heart failure, arrhythmias, and sudden cardiac death.[4,28] Heart failure can occur in both the early and the late postoperative periods.

In children with TGA, the aim of the Jatene procedure is to reconstruct the normal anatomic relationship of the aorta, pulmonary artery (arterial switch), and coronary arteries. This type of operation is not free of residual lesions and complications that affect the state of patients; in the appearance of heart failure, the most important etiology may be a narrowing of transplanted coronary arteries and progressive impairment of myocardial perfusion.[6,29] It has been documented in animal models that even denervation alone of the transplanted coronary arteries may lead to reduced perfusion of the myocardium. Studies conducted many years after the Jatene operation disclosed, in some patients, reduced hemodynamic parameters of the left ventricle. A useful and proper test in this situation is the test with dobutamine.[30]

The Fontan operation is performed in children with a single-chambered heart. It involves systemic venous connection with the pulmonary artery system. The types of cardiovascular defects and changes are the cause of postoperative residual lesions and complications. Increased pressure in the venous system can lead to swelling, transudates, or blood clots. Late

complications are arrhythmias, thromboembolic events, exudative enteropathy, progressive ventricular dysfunction, liver dysfunction, and many others.

Exercise capacity in these children depends on the type of defect and type of operation. The existence of a single operative chamber, which is in fact a chamber system, and the absence of ventricularly pumped blood to the lungs results in a lack of pulsed blood flow through the lungs. This results in worse performance parameters, including lowered VO2 and increased levels of NT-proBNP.[7,17] Achieving VO2 values below 50% of the predicted normal results already indicates heart failure.

By analyzing information from interviews with patients postoperation, it can be assumed that efficiency is influenced by lifestyle and physical activity. Many surgical patients (especially children) do not perform any physical activity and effort, even in everyday life. It seems that parents and teachers too quickly and too easily release the children from even minimal exertion. This inevitably leads to a reduction in exercise capacity.[17] Many scientific papers present the results of conducting physical training and training in patients after surgery to treat congenital heart defects: they respond to training similar to a healthy person.[31,32] Increased physical performance is reflected in better endurance performance, including higher VO2 values.

Even short-term training leads to better efficiency parameters that persist for a long time.[9] In addition, the training does not lead them to the adverse remodeling.[32] It is interesting that the children, after surgery for ToF or TGA, assess their quality of life as similar to healthy children, even slightly overestimating their abilities.[33] Therefore, they should be covered by professional care rehabilitation. Appropriate training may be an inexpensive and efficient way to improve cardiovascular and related exercise capacities.[33–35]

In contrast, for patients after the Fontan operation, an almost complete limitation of physical activity was recommended until quite recently; however, there were reports of the beneficial effects of exercise training on cardiac output. Also, exercise under control and professional training improves physical performance and slows down the time to reduced effort.[32,36,37]

In general, based on our results, we cannot tell which parameter, VO2 or NT-proBNP, better evaluates cardiovascular status and exercise capacity; however, surely denoting both are possible to obtain a more complete and accurate picture of the patient's clinical status. Each of these tests has its advantages. VO2 is considered the best parameter for assessment of exercise capacity, while NT-proBNP is useful in the early stages of heart failure, when NT-proBNP values are elevated.[38]

Our work has limitations. The most important is that the group of children after the Fontan operation method was too small and not representative for statistical analysis. In contrast, a trend can be observed that the children of this group achieve the worst results of heart failure after surgery. Therefore, we will continue to investigate this topic.

CONCLUSIONS

Children, after operations to treat complex heart defects, such as ToF, TGA, and SV, have worse exercise capacity parameters than healthy children.

It is highly probable that the poor exercise capacity is the result of not only the presence of residual lesions but also lower physical activity. Improved efficiency can be achieved by eliminating or reducing residual amendments and performing exercise training under adequate professional care. In the postoperative follow-up, these children should undergo ergospirometric tests and the levels of NT-proBNP should be evaluated.

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