CLINICAL STUDY

Predictors of exercise capacity in patients with atrial correction of transposition of great arteries

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ABSTRACT

OBJECTIVES: To examine the relationship of clinical, biochemical and imaging parameters to maximum oxygen uptake in patients after atrial correction of transposition of great arteries.

BACKGROUND: Exercise tolerance is a key determinant of quality of life in patients with adult congenital heart disease. It is determined by a large scale of factors often different from general cardiology.

METHODS: 86 consecutive patients after Senning correction of TGA were subjected to clinical and echocardiographic examination, Holter monitoring, blood tests of NT-proBNP, MRI of the heart and exercise test. Parameters of these examinations were correlated to VO_2 max.

RESULTS: The average age of patients was 28±3.5 years. The average systemic right ventricular function determined by MRI was 51.9±7.9 %. The average NT-proBPN was 124.3±23.6 ng/l, VO_2 max. 31.7±6.5 ml/kg/min and the heart rate reserve 106±24 /min. Neither systemic right ventricular systolic function nor NT-proBPN predicted VO_2 max., whereas the heart rate reserve did (p=0.003).

CONCLUSION: An inability to increase heart rate during exercise noted in a considerable number of patients after atrial switch of TGA caused a decreased exercise tolerance. It is not solely the global systolic function of either ventricle that influences the exercise performance, rather it is the ability to increase heart rate and overall cardiac output appropriately *(Tab. 3, Fig. 6, Ref. 28)*. Text in PDF *www.elis.sk*

KEY WORDS: transposition of great arteries, Senning correction, maximal oxygen uptake, right ventricular systolic function, heart rate reserve.

Introduction

It is generally known that patients after Senning (atrial) correction of transposition of great arteries (TGA) survive well into adulthood. The expected long-term mortality is acceptable, with the survival rates reaching 75 % at 30 years follow up (1, 2, 3). Patients´ morbidity and quality of life are determined largely by an exercise tolerance (4). There is an interest in investigating systemic right ventricular systolic function (RVEF) and its influence on exercise and functional capacity (5, 6, 7, 8, 22). The attention also focuses on other pathophysiologic mechanisms influencing

exercise tolerance such as: atrial baffles capacitance and diastolic function of both ventricles (9, 10). Potential predictors of low functional capacity and cardiac insufficiency as B-type natriuretic peptide (NT-proBNP) and other markers have been investigated. Nevertheless, none of above the mentioned parameters showed a consistent relationship to exercise tolerance throughout available literature data. Our aim was to evaluate a set of clinical, biochemical and imaging parameters that can be easily accessible in daily clinical practice and examine their association with the maximal oxygen uptake (VO_2 max.), when evaluating the exercise capacity.

Materials and methods

86 consecutive patients after Senning correction of TGA in childhood, presenting for a regular examination in the outpatient service of the Center for Adults with Congenital Heart Disease at the University Hospital Motol in Prague within the period of one year, were subjected to clinical and echocardiographic examination, Holter monitoring, blood tests of NT-proBNP, MRI of the heart and the exercise test. Their median age at operation was 0.62 years and the median age at follow-up examination was 27.2 years. Patients with permanent cardiac pacemakers were excluded from the study due to the inability to undertake cardiac MRI. The study was approved by the hospital ethical committee and all the patients signed an informed consent.

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Tab. 1. Patient demographic and clinical characteristics.

Female sex, n (%)	22 (25.6%)
Age at operation, y, mean (SD)	1.42 (0.86)
Age at operation, y, median	0.62
Age at clinical examination, y, mean (SD)	28 (3.5)
Age at clinical examination, y, median	27.2
NYHA class, mean (SD)	1.3 (0.44)
NT-proBNP (ng/l), mean (SD)	124.3 (23.59)

Tab. 3. Correlation coefficients for VO$_2$ max and given parameters.

Parameter	ρ value	p value
NT-pro BNP	0.0706	0.608
NYHA		0.037
RVEF echo		0.029
RVEF MR	0.0752	0.502
LVEF MR	0.1295	0.282
HRR	0.3247	0.003

RVEF – right ventricular ejection fraction; LVEF – left ventricular ejection fraction; MR – magnetic resonance; HRR – heart rate reserve

Clinical examination and diagnostic tests

A detailed history focused on functional status and the quality of life. New York Hospital Association functional class was recorded. A thorough questioning and examination for signs and symptoms of cardiac insufficiency was performed. All medications were noted. Blood tests for NT-proBNP were drawn. Standard Holter ECG 24- hour monitoring was performed and the presence of disorder of sinus node function presented as either junctional rhythm or ectopic atrial rhythm was recorded.

Echocardiography

Echocardiography was performed on Vivid 9 analyser (GE Medical Health Systems) with 2.5–5 MHz convex transducers by one experienced examiner. Transthoracic examinations were performed in supine position using standard 2D grayscale and Doppler techniques. All measurements were performed in standard projections in compliance with American Society of Echocardiography guidelines. Right ventricular systolic function was assessed semi-quantitatively and characterized as good, when the estimated ejection fraction was above 50 %, moderately impaired (35–50 %) and severely impaired (less than 35 %). Systemic tricuspid valve regurgitation was graded as mild, moderate or severe.

MRI

All examinations were performed on 1,5T MRI Avanto equipment. Standard protocol included static steady-state free procession (SSFP) in axial, coronal and sagittal planes, cine SSFP and contrast enhanced angiography. For volume measurements, consecutive cine SSFP retrospectively gated images were used (slice thickness 8 mm, gap 2 mm, 25 phases). Manual delineation of the endocardial borders was performed in end-diastole and end-systole. Ejection fraction (EF) was calculated as (End Diastolic Volume-End Systolic Volume/ End Diastolic Volume) and expressed in percent for both systemic right and sub-pulmonary left ventricles.

Exercise testing

Exercise testing was conducted on electromagnetically braked bicycle ergometer (Ergoselect 100P, Ergoline, Bitz, Germany).

Standardised protocol with 0.5 Watt/kilogram increments every three minutes was performed. Respiratory gas analysis of the breath was performed using a properly calibrated gas analyser Oxycon Pro with electrochemical oxygen sensor (CareFusion, Hoechberg, Germany). Heart rate and ECG were monitored continuously. At each step of exercise, peripheral capillary oxygen saturation, heart rate, blood pressure and ECG were registered. Exercise was terminated at the limit of patients staying power, but patients were strongly encouraged to continue with exercise till there was an evidence of anaerobic metabolism. None of the patients had to terminate exercise due to chest pain, arrythmia or descent of systolic blood pressure. The maximal workload relative to body weight, maximal oxygen uptake, and heart rate reserve were recorded. Heart rate reserve (HRR) was calculated as the heart rate at peak exercise minus resting heart rate.

Statistical analysis

Continuous data are reported as the means±SD and medians and the range and categorical variables as counts and percentages. Student's tests were performed for paired comparisons, when data was normally distributed. The analysis of relations among the studied variables was performed using non-parametric statistical methods such as: Kruskal-Wallis ANOVA, Mann–Whitney test, Fisher exact test and Spearman correlation coefficient. Analysis was performed in R statistical software, version 3.4.2, R Core Team (2017). p-values less than 5 % were considered statistically significant (11).

Results

The average age of the patients at examination was 28±3.5 years, their median age was 27.2 years and 74 % were men. NYHA I class was reported by 63 (73 %) of patients, NYHA II by 22 (26 %) and only one patient stated NYHA class III (Tab. 1). Holter monitoring detected episodes of junctional or ectopic atrial rhythm in 45 % of patients and none atrioventricular block. Right ventricular function determined by echocardiography was normal in 52 (60.1 %) patients, moderately decreased in 31 (36.5 %) and only in three (3.4 %) patients it was classified as severely decreased. MRI diagnosed 2 patients (2.2 %) with a severely decreased right ventricular function, 36 (36 %) with a moderately decreased function and in 48 (55.8 %) patients, the right ventricular function was
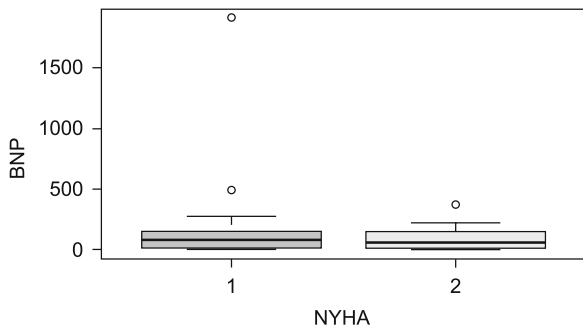
Tab. 2. Echocardiographic and MRI parameters of systemic right ventricle systolic function.

	Good, n (%)	Moderately impaired, n (%)	Severely impaired, n (%)
Echocardiography	52 (60)	31 (36)	3 (3.4)
MRI	48 (55,8)	36 (36)	2 (2.3)

The right ventricular systolic function was assessed semi-quantitatively by echocardiography and characterized as good, when the estimated ejection fraction was above 50 % , moderately impaired (35 – 50 %) and severely impaired (less than 35 %). The same criteria were used for MRI assessment of right ventricular systolic function.

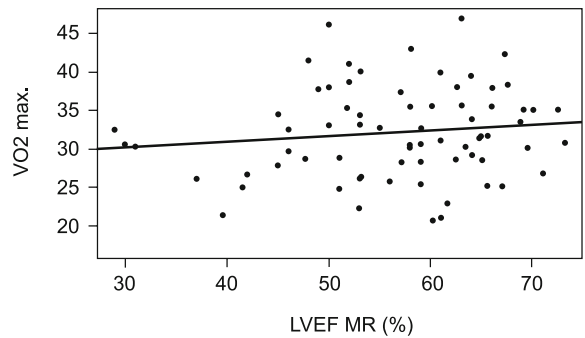**Fig. 1. Relation of NYHA to NT-proBNP.**

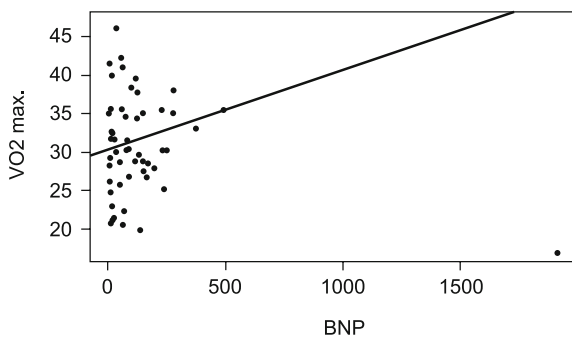**Fig. 5. Relation of MRI LVEF to VO$_2$ max.**

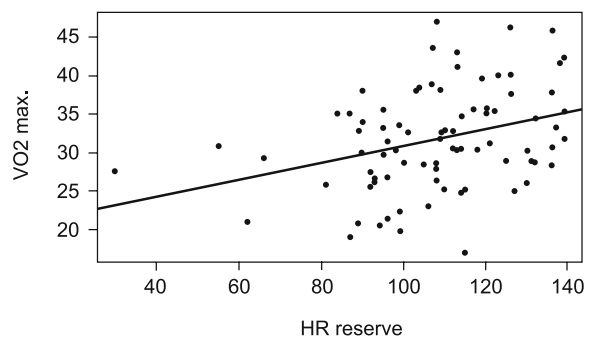**Fig. 2. Relation of NT-proBNP to VO$_2$ max.**
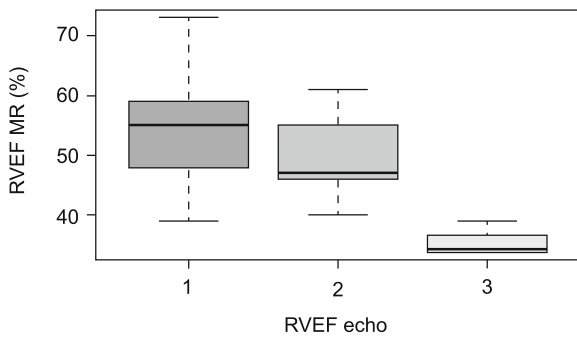

Fig. 6. Relation of heart rate reserve (HRR) to VO$_2$ max.

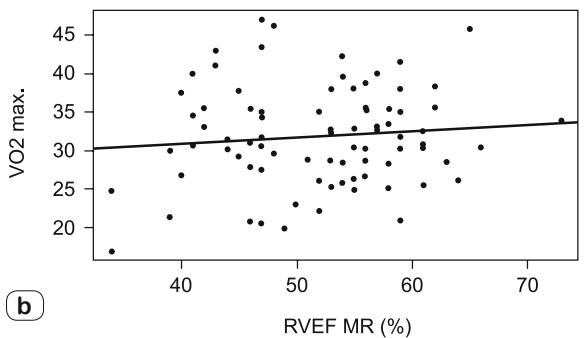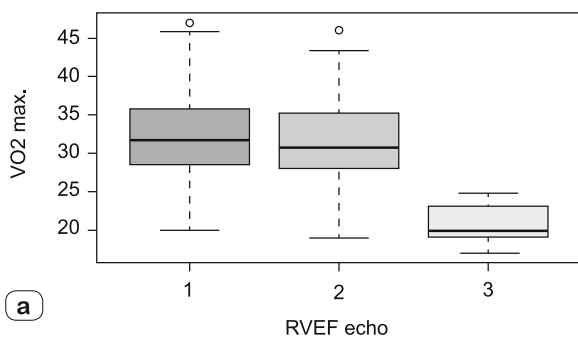**Fig. 3. Comparison of systemic right ventricular function assessed by echocardiography and MRI.**

normal (Tab. 2). The mean systemic right ventricular function assessed by MRI was 51.9±7.9 %, whereas the mean subpulmonal left ventricular function was 56.7±9.9 %. The mean NT-proBNP was 124.3±23.59 ng/l, elevation of this marker above 450 ng/l was present only in two patients and just one patient already listed for heart transplantation presented with NT-proBNP value above 1000 ng/l. The mean VO$_2$ max during exercise was 31.7±6.5 ml/kg/min. 12 patients were found to be in the range below 1 standard deviation (SD) and one ranked below 2 SDs range. The mean heart rate reserve was 106±24/min.

NT-proBNP did not predict neither NYHA class (p=0.81) nor VO$_2$ max (ρ=0.0706, p=0.60) (Figs 1 and 2). The ejection fraction of the systemic right ventricle estimated by echocardiography cor-

a

b

Fig. 4 a, b. Relation of echocardiographic and MRI RVEF to VO$_2$ max.

related well with the one calculated by MRI (Fig. 3). Echocardiography however tended to slightly overestimate EF. (Comparison of groups (Kruskal-Wallis test): p=0.001 Test of independence (Fisher´s exact test): p=0.037)).

The right ventricular function assessed by echocardiography in semiquantitative mode predicted VO$_2$ max (Comparison of groups (Kruskal-Wallis test): p=0.03)), whereas the ejection fraction in percentage described by MRI did not correlate with VO$_2$ max. (Spearman´s correlation coefficient: ρ=0.07, p=0.502) (Figs 4 a,b) . The ejection fraction of the left subpulmonary ventricle did not correlate with VO$_2$ max either (Spearman´s correlation coefficient: ρ=0.13, p=0.28) (Fig. 5). The heart rate reserve was the only parameter that statistically correlated with VO$_2$ max. (Spearman´s correlation coefficient: ρ=0.32, p=0.003) (Fig. 6).

Discussion

Maximal oxygen uptake is perceived to be a core parameter of exercise tolerance and capacity. It predicts survival in patients with a systemic left ventricular dysfunction (12). The same relationship has not been proven for the right ventricle in the systemic position. However, the exercise capacity and functional class are among the most important predictors of the quality of life of patients with congenital heart disease including TGA after atrial correction (13). We sought to examine, which of routinely used fundamental clinical, biochemical and diagnostic parameters in the patients with systemic right ventricle including NYHA class, NT-proBNP, echocardiographic a MRI derived RVEF and HRR would be statistically associated with VO$_2$ max. Our one-year study comprised the follow up of all consecutive patients after Senning correction of TGA. Patients with permanent pacemakers did not participate in the study as they could not had undergone MR examination of the heart.

It was not surprising that no correlation of NYHA class to VO$_2$ max was observed. NYHA is a subjective measure of shortness of breath and fatigue, when performing activity. Our finding may reflect CHD patients´ habitual limitation of being acclimated to low exercise tolerance, which they do not perceive as unusual. Lifelong living with CHD downgrades a person's expectation as to what "normal activity" means. Also, a restriction of physical activity by parents, care-takers and teachers plays an important role as a possible confounder, when assessing NYHA class by patients. Unfortunately, the same is valid for the ability index sometimes used as an alternative of NYHA, when assessing the functional capacity in Adult Congenital Heart Disease population (14).

NT-proBNP is a known predictor of short and long- term mortality in TGA (15) and in other congenital heart diseases as well (23). Unexpectedly, we found that the average and median values of NT-proBNP in TGA population were heterogenous throughout the published literature. Our observed NT-proBNP values were low, when compared to Popelova et al (15), who reported the mean value of 203 ng/l and were higher than those reported by Plymen et al (6), where the mean NT-proBNP was 40±35 ng/l. Indeed, the span of values stated in literature for the same age group of TGA atrial switch patients was surprisingly broad. The number of NT-proBNP values exceeding the generally accepted threshold for cardiac insufficiency in our study was low. Finally, NT-proBNP in our study did not correlate with VO$_2$ max.

The ejection fraction of systemic right ventricle is generally assumed to be the fundamental parameter determining the exercise capacity in TGA after an atrial switch – analogous to the left ventricle in patients with a conventional left sided heart failure. We assessed the systolic function semi-quantitatively by echocardiography and more precisely by MRI computation. Both measurements correlated well one to another despite echocardiography tending to slightly overestimate the EF. The systemic right ventricular function in our study assessed by MRI was good in concordance with the findings reported by other investigators – Plymen et al (6) – 51.4±7 %, LaRocca et al (7) – 56±7 % and Lorenz et al (16) – 51±9 %.

Overall, the systemic RV function assessed semi-quantitatively by echocardiography correlated well with VO$_2$ max, while measurements provided by cardiac MRI did not. This finding is in concordance with Helsen et al (5), Samarai (26) and LaRocca et al (7), where RVEF did not predict VO$_2$ max either. Nonetheless, it is in contrary to Gavotto (28) and Buys et al (17), where „type of surgery, total energy expenditure and right ventricular contractility were independent predictors of peak VO$_2$". Our ambivalent findings thus contribute to the large amount of controversial literature data attempting to investigate hypothesis, whether the systemic right ventricular systolic function determines the maximal oxygen uptake. The final verdict still remains to be pronounced. Possibly, a more complex echocardiographic assessment including longitudinal function parameters, ie. global longitudinal strain and 3D volumetric function parameters should be employed into comprehensive evaluation of the patients with the systemic right ventricle (27).

Systolic left ventricular function was normal in our cohort and also in other reports in literature (7, 16). As the cardiac output of systemic right ventricle (2.5±0.8 ml) and left ventricle end diastolic volume (LVEDV) were significantly lower than in the control group in Buys et al (17), we can speculate that filling patterns and atrial baffle capacitance (primary determinants of diastolic filling) and preload might also play an important role in influencing cardiac output and overall exercise capacity as reported by Reich and others (10, 18, 9).

The most striking finding emerging from our study was that exercise capacity of our patients compared to scores reported in literature was higher than in other cohorts – the study from Inuzuka et al (21) mentioned the average VO$_2$ max. 24.2±7.5 ml/min/kg at age 26.5 years. LaRocca et al (7) found VO$_2$ max. of 23±4 ml/min/kg and Li reported 27.8±7.6 ml/min/kg in their cohorts. Our reported VO$_2$ max. is by 32 % higher. The average normal values for the same age group in a normal healthy population were 42–46 ml/min/kg in men and 38–41 ml/min/kg in women. Our patients reached 77.3 % of these normal values compared to 66 % reported by Inuzuka et al (21) and 64 % by Buys et al (17).

It is well-known that the sinus node disorder is inherent to the status post atrial correction and its prevalence ranges in the published literature from 27 % (19) to 52.8 % (20). During Holter

ECG monitoring, we detected that 45 % of our patients had the sinus node disorder presenting either as episodes of atrial or junctional rhythm with ensuing inability to increase heart rate adequately during a physical load. It is a logical assumption that inability to appropriately increase heart rate influences an overall exercise capacity. Heart rate reserve was a predictor of VO_2 max in our study. Based on results of our study and our practical experience with the patients with an incorrect pacemaker settings who can – only after a correct adjustment – increase their heart rate during the exercise testing appropriately and only then does their exercise tolerance improve, we propose that inability to increase heart rate is a limiting factor of exercise tolerance. This suggests that not just the stroke volume, but overall heart output influences the exercise capacity.

Conclusion

The long-term results of the follow up of the patients after Senning correction of TGA were good. More than a half of the patients in our study presented with a systemic right ventricle systolic function in the normal range, while a severe impairment was noted in a small number of patients. The ejection fraction of the systemic right ventricle did not correlate with VO_2 max. The mechanism of a decreased exercise capacity in the patients after an atrial switch is probably complex comprising not only the systolic function of right ventricle, but also intricate haemodynamics of a limited flow through atrial baffles and ensuing a diastolic dysfunction of both ventricles. We were able to demonstrate that a chronotropic incompetence presenting as inability to increase the heart rate during the exercise noted in a considerable number of patients after an atrial switch of TGA was one of the causes of a decreased exercise tolerance. Based on our work, we conclude that it is not only systolic function of either ventricle that influences the exercise performance, rather it is the ability to increase the heart rate and overall cardiac output appropriately.

Limitations

Patients with permanent pacemakers were excluded from the study due to inability to undergo MRI of the heart. 2 patients listed for heart transplantation followed-up at a different cardiology centre were not included in the study. Only patients coming for the regular outpatient follow up were included. This could have influenced the results of the study by narrowing the range of NT-proBNP values and VO_2 max noted in our cohort by unintentionally excluding patients, who would not had come for regular visit due to medical disability.

Learning points

Exercise tolerance is a key determinant of the quality of life in adult congenital heart disease patients.

The systemic right ventricular ejection fraction remains moderately decreased in a majority TGA patients after Senning correction.

The systolic function of the systemic right ventricle does not predict the maximum oxygen uptake.

An inability to increase the heart rate appropriately during an exercise is the limiting factor of the exercise tolerance in TGA patients after an atrial correction.

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