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Influence of percutaneous pulmonary valve implantation on exercise capacity: Which group of patients benefits most from the intervention?

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Abstract

Background: *The aim of the study was to evaluate the role of cardiopulmonary exercise testing (CPET) parameters in assessing exercise capacity improvement after percutaneous pulmonary valve implantation (PPVI). Additionally, it aimed to determine if there are any baseline characteristics influencing that change.*

Methods and results: *The study comprised 32 patients (mean age 26 ± 9); 53% males; diagnosis: tetralogy of Fallot (n = 18), pulmonary atresia (n = 6), Ross procedure (n = 4), other (transposition of great arteries, pulmonary stenosis, double outlet right ventricle, common arterial trunk type II — n = 4) who underwent successful PPVI due to right ventricular outflow tract dysfunction (predominant pulmonary regurgitation — n = 17, predominant pulmonary stenosis — n = 15). Treadmill CPET was performed before and a year after PPVI along with clinical evaluation, cardiac magnetic resonance and transthoracic echocardiography. Twelve months post successful PPVI (pulmonary valve competence restoration and pulmonary gradient reduction from 58.8 ± 47.1 to 26.6 ± 10.8 mm Hg) there was a significant decrease in the ventilatory equivalent for CO_2 at peak exercise ($EQCO_2$) (25.3 ± 3.3 to 24.3 ± 3.0, p = 0.04) and oxygen consumption at peak exercise (pVO_2) (20.4 ± 5.0 to 22.6 ± 5.3 mL/kg/min, p = 0.04). Improved $EQCO_2$ correlated with an increase in right and left ventricular ejection fraction (respectively R = –0.57, p = 0.002; R = –0.56, p = 0.002). In this study, no baseline factors that might affect improvement in exercise function were found.*

Conclusions: *Successful PPVI leads to an improvement in exercise capacity and hemodynamic response to exercise. The correlation between the improvement in $EQCO_2$ or peak VO_2 and baseline characteristics was too weak to reliably identify the group of patients that will benefit from the procedure.* (Cardiol J 2015; 22, 3: 343–350)

Key words: percutaneous pulmonary valve implantation, cardiopulmonary exercise testing, grown up congenital heart disease

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Introduction

Patients with certain types of congenital heart defect need to undergo surgical repair of right ventricular (RV) outflow tract (RVOT) in their early infancy. After some years, the implanted RVOT conduits almost inevitably degenerate causing RV obstruction and/or regurgitation, which leads to progressive dysfunction of the RV requiring further surgical interventions. Consequently, those patients need to be subjected to multiple surgeries, each connected with an increasing risk. Percutaneous pulmonary valve implantation (PPVI) is a promising alternative for this group of patients. Some improvement of hemodynamic parameters after the procedure has been reported in several trials [1–4]. However, it is difficult to determine optimal timing for the intervention. Impaired physical capacity is reported to be the one of the first signs of decline in the RV function in asymptomatic patients [5, 6]. The aim of this study was to investigate whether PPVI leads to an improvement in exercise function and which patients might benefit from the procedure when assessed with selected cardiopulmonary exercise testing (CPET) parameters.

Methods

Patient selection

It is a retrospective cohort study. Out of 37 consecutive patients who underwent successful PPVI in the Institute of Cardiology in Warsaw, Poland, in years 2008–2012, 32 patients were investigated. The qualification of patients included: clinical examination, transthoracic echocardiography (TTE), cardiovascular magnetic resonance (CMR) and CPET performed before and 1 year after PPVI. Five patients were excluded due to inappropriate CPET performance (different protocol for a particular subject has been used before and after PPVI).

The study group consisted of 17 men and 15 women who underwent surgical repair of congenital heart defect in the past and were qualified for PPVI due to pulmonary valve dysfunction. The group was divided into two subgroups basing on the type of dominant lesion. Group 1 consisted of patients with predominant pulmonary stenosis (PS), significant pulmonary gradient, the pulmonary regurgitation fraction (PRF) < 25%, and maximally mild PR in echocardiography. Group 2 consisted of patients with predominant pulmonary regurgitation (PR), PRF ≥ 25% or significant PR in echocardiography. Inclusion criteria for PPVI were based on surgical indications for RVOT reoperation [7]. Percutaneous pulmonary valve implantation using either Melody® valve (n = 20) or SAPIEN™ THV (n = 12) was performed according to the protocol described previously [1, 8].

Study protocol

The study was approved by the local Research Ethics Committee. CPET, CMR and TTE were performed 1 day – 5 months before PPVI and 1 year after the procedure along with the assessment of the New York Heart Association (NYHA) functional class. Each subject gave a signed informed consent.

Cardiopulmonary exercise testing

Cardiopulmonary exercise treadmill test was performed approximately 2 h after medications and a light breakfast in all patients. Each subject performed a symptom limited CPET according to a Ramp protocol or modified Bruce protocol (always the same protocol for a particular subject before and after PPVI so that each patient would be a control for him/herself). The test was performed using a Schiller treadmill (Carrollton, USA) which was connected to a computerized breath-by-breath spiroergometry system (ZAN 600, ZAN Messgeräte GmbH, Germany).

Oxygen consumption (VO_2) was measured continuously using breath-by-breath analysis and used as an index of exercise capacity. Peak VO_2 was defined as the highest oxygen uptake level achieved during the final 30 s of CPET. The formula used for the prediction of VO_2 (in mL/kg/min) was the Wasserman standard calculation, which incorporates sex, age, height, and weight of the subject and is valid for patients aged over 20 years [9]. Twelve-lead electrocardiogram (ECG) and heart rate (HR) were recorded continuously at rest, during CPET and during recovery until HR, ECG, and VO_2 returned to the baseline values. Blood pressure (BP) was measured manually every 2 min using a sphygmomanometer.

Subjects were encouraged to exercise until they reached a self-determined limit of their functional capacity (perceived exertion or dyspnea) or until a physician terminated the test according to the European Society of Cardiology guidelines [10].

All CPET procedures were supervised by a nurse and a cardiologist. The parameters measured were the duration of workload, peak VO_2 [mL/kg/min], % predicted peak VO_2, minute ventilation (VE [L/min]), respiratory exchange ratio, HR [bpm], BP [mm Hg], breathing frequency [L/min], and ventilatory equivalents for CO_2 ($EQCO_2$).

Table 1. Demographic data.

Parameter		Total population (n = 32)
Age [years]		26 ± 9
Body mass index [kg/m^2]		21.5
Sex (male/female)		17/15
Baseline NYHA:	I	8
	II	15
	III	9
	IV	0
Baseline diagnosis:	Tetralogy of Fallot	18
	Pulmonary atresia	6
	Aortic valve stenosis, Ross procedure	4
	TGA, Rastelli procedure	1
	Pulmonary stenosis	1
	Double outlet right ventricle	1
	Common arterial trunk type I	1
Valve implanted:	Melody® valve	20
	SAPIEN™ THV	12
Predominant lesion:	Stenosis	15
	Regurgitation	17

NYHA — New York Heart Association functional classification; TGA — transposition of great arteries

Cardiovascular magnetic resonance

The data derived from CMR were collected using a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany). The acquisition included steady-state free precision images in left ventricle (LV) long axis (2-, 3- and 4-chamber views) as well as a stack of short axis cross sectional views covering the ventricles from base to apex and phase contrast flow according to the instructions described previously [11]. After manual determination of end-diastolic and end-systolic endocardial outline, dedicated software (MASS 6.2.1, Medis, Leiden, the Netherlands) was used to assess RV and LV volumes and sizes. All volumes were indexed by body surface area (BSA) and expressed in mL/m^2. The degree of PRF was calculated with the dedicated software (Argus, Siemens, Erlangen, Germany).

Transthoracic echocardiography

Transthoracic echocardiography was performed using an echocardiographic system (Vivid 7, GE Medical Systems, Milwaukee, USA). The degree of RVOT gradient was derived from the peak velocity obtained by continuous-wave Doppler using the modified Bernoulli equation. Pulmonary regurgitation was evaluated on the basis of vena contracta. The regurgitant jet exceeding 6 m in width was found to be significant. The remainder was considered to be small or moderate.

Statistical analysis

All continuous variables are expressed as mean ± standard deviation. Paired Student's t-test was used to compare changes in CPET, CMR, TTE parameters for normally distributed variables before and after PPVI. Non-normally distributed variables were compared with the aid of the Signed Rank test. The normality of distribution was assessed using the Shapiro-Wilk test. Correlations between changes in CPET parameters and (a) baseline CMR and TTE parameters, (b) changes in CMR and TTE were tested using Pearson's test. The level of significance was defined at $p < 0.05$. All statistical analyses were performed with the use of MedCalc 10.0.2.0 statistical software (MedCalc, Mariakerke, Belgium).

Results

The patients' characteristics are shown in Table 1. Thirty-two patients met the inclusion criteria for the study. The mean age at the study onset was 26 ± 9 years; 17 patients were diagnosed with predominant regurgitation, 15 with predominant stenosis. The most common primary diagnosis was tetralogy of Fallot (56%) followed by pulmonary atresia (n = 6), aortic valve disease (Ross procedure) (n = 4), transposition of great arteries (n = 1), pulmonary stenosis (n = 1), double outlet RV (n = 1), common arterial trunk

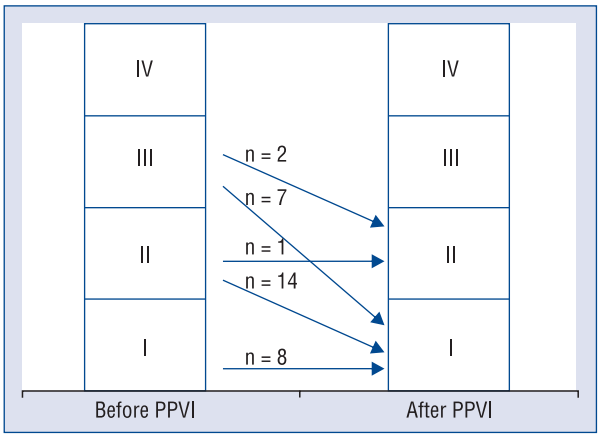

Figure 1. New York Heart Association (NYHA) functional class before and after percutaneous pulmonary valve replacement (PPVI); n — number of patients.

type I (n = 1). The patients had an average of two surgeries prior to PPVI. The mean time since the last intervention was 14.7 years. PPVI led to valve competence restoration observed in all patients 1 day after the procedure.

In the subgroup of patients with significant PS, pulmonary gradient decreased from 94.5 (range 41–200) to 38.9 (range 22–68). These results remained stable in a 1-year observation.

Additionally, we detected a statistically significant decrease in RV end-diastolic volume (RVEDV) and end-systolic volume (RVESV) and an increase in RV ejection fraction (EF) (p = 0.003; p = 0.0003; p = 0.008, respectively). When comparing the group of patients with PS with patients with PR, it appeared that the statistically significant decrease in RVEDV was noted in the latter group only. The end-diastolic volume of LV and LVEF increased (respectively $p < 0.0001$; p = 0.04).

Twelve months after PPVI no worsening in NYHA functional class was observed in any patient.

Furthermore, every symptomatic patient (with NYHA functional class II or above) who underwent the procedure improved in his/her functional class. The remaining 8 asymptomatic patients claimed significant improvement in physical capacity (Fig. 1).

PPVI led to a statistically significant increase in peak VO_2 (20.4 ± 5.0 vs. 22.6 ± 5.3 mL/kg/min; p = 0.04) (Fig. 2A). There was also a reduction in $EQCO_2$ at peak oxygen uptake (25.3 ± 3.3 vs. 24.3 ± 3.0; p = 0.04). After comparing PR and PS groups, a statistically significant reduction in $EQCO_2$ was observed only in PS group (25.1 ± ± 2.5 vs. 23.4 ± 2.4; p = 0.03) (Fig. 2B). Systolic BP at maximal effort increased after the procedure (135.8 ± 26.3 vs. 154.1 ± 29.5 mm Hg; $p < < 0.0001$). The duration of workload was elongated after the intervention (621 ± 204 vs. 676 ± 182 min; p = 0.0004).

There was no correlation between improvement in peak VO_2 and either of the examined baseline CMR or TTE characteristics (Table 2).

An improvement in $EQCO_2$ (lower values of $\Delta EQCO_2$) correlated with baseline: greater mass of RV or LV, higher RVOT maximal gradient and PRF (R = –0.38; p = 0.047; R = –0.35; p = 0.06; R = –0.46; p = 0.01; R = –0.35; p = 0.08, respectively) (Table 2). The primary outcome defined as an improvement in $EQCO_2$ (decrease in $EQCO_2$

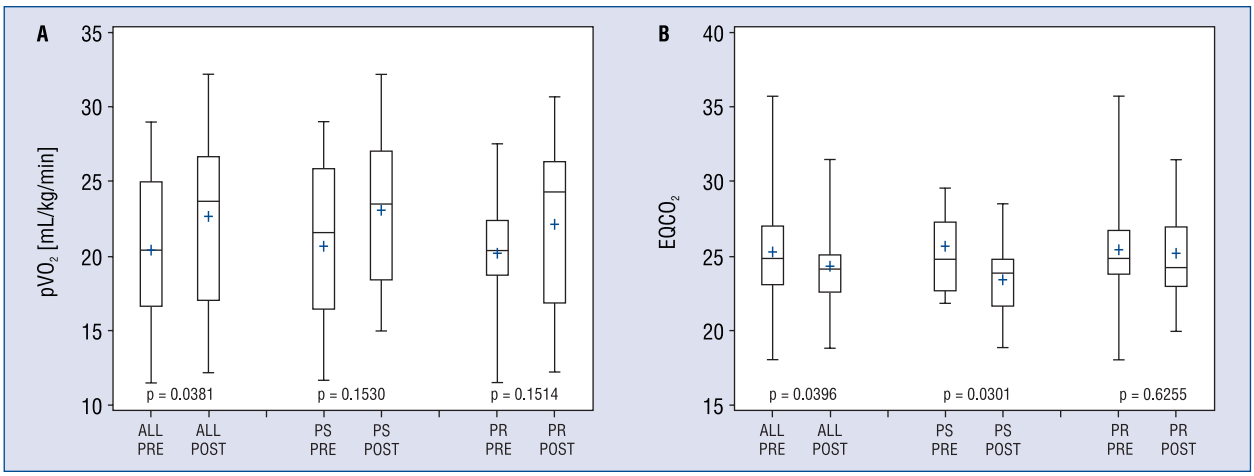

Figure 2. Results of peak oxygen uptake (pVO_2) and ventilatory equivalent for oxygen consumption ($EQCO_2$) before and 12 months after percutaneous pulmonary valve replacement (PPVI); PS — predominant stenosis; PR — predominant regurgitation.

Table 2. Relationship between change in peak oxygen consumption (VO_2) and ventilatory equivalents for CO_2 ($EQCO_2$) and baseline magnetic resonance imaging and echocardiography parameters.

	ΔpVO_2			$\Delta EQCO_2$		
	N	R	P	N	R	P
Right ventricular end-diastolic volume index [mL/m^2]	28	0.25	NS	28	0.07	NS
Right ventricular end-systolic volume index [mL/m^2]	28	0.17	NS	28	0.04	NS
Right ventricular ejection fraction [%]	28	–0.07	NS	28	0.19	NS
Right ventricular mass [ml/m^2]	28	0.13	NS	28	–0.38	**0.047**
Left ventricular end-diastolic volume index [mL/m^2]	28	–0.23	NS	28	–0.17	NS
Left ventricular end-systolic volume index [mL/m^2]	28	–0.08	NS	28	–0.18	NS
Left ventricular ejection fraction [%]	28	–0.13	NS	28	0.14	NS
Left ventricular mass [mL/m^2]	28	–0.24	NS	28	–0.35	**0.06**
Right ventricular outflow tract maximal gradient	28	–0.04	NS	28	–0.46	**0.01**
Pulmonary regurgitation fraction [%]	26	–0.03	NS	26	–0.35	**0.08**

N — number of patients; R — Pearson correlation coefficient; Δ — indicates change (from baseline to 1 year post implantation); NS — statistically non-significant change or no trend; Bold indicates statistically significant change or trend

Table 3. Univariate regression analysis of potential predictors of changes inpeak oxygen consumption (VO_2) uptake and ventilatory equivalents for CO_2 ($EQCO_2$).

	ΔpVO_2			$\Delta EQCO_2$		
	N	R	P	N	R	P
Δ Right ventricular end-diastolic volume index [mL/m^2]	28	–0.35	**0.07**	28	0.12	NS
Δ Right ventricular end-systolic volume index [mL/m^2]	28	–0.25	NS	28	0.20	NS
Δ Right ventricular ejection fraction [%]	28	0.02	NS	28	–0.57	**0.002**
Δ Right ventricular mass [mL/m^2]	26	–0.15	NS	26	0.27	NS
Δ Left ventricular end-diastolic volume index [mL/m^2]	28	0.09	NS	28	–0.01	NS
Δ Left ventricular end-systolic volume index [mL/m^2]	28	0.06	NS	28	0.43	**0.02**
Δ Left ventricular ejection fraction [%]	28	–0.01	NS	28	–0.56	**0.002**
Δ Left ventricular mass [mL/m^2]	27	0.40	**0.04**	27	0.36	NS
Δ Right ventricular outflow tract maximal gradient	27	0.10	NS	27	0.44	**0.02**

N — number of patients; R — Pearson correlation coefficient; Δ — indicates change (from baseline to 1 year post implantation); NS — statistically non-significant change or no trend; Bold indicates statistically significant change or trend

after the procedure) correlated significantly with an increase in EF of the RV and LV (Table 3).

Discussion

Optimal timing for the intervention in patients with RVOT dysfunction has been widely debated. The group of patients subjected to PPVI is varied in terms of primary diagnosis, symptoms, number of interventions, type of dominant lesion, and anatomy of the heart. Investigators try to define the baseline characteristics related to an improvement after PPVI, most typically acknowledged by the assessment of ventricular end-systole and end-diastole volumes, or CPET [11–14]. The reported factors that are believed to influence short- and/or long-term results include: type of dominant lesion [4, 15]; baseline RVEDV [16, 17]; and baseline peak VO_2 value [18]. In this study, no baseline factors that might affect an improvement in exercise function were found. This, however, might be due to small, heterogeneous patient group, therefore further research is needed.

Previous studies remain unequivocal about the influence of PPVI on exercise performance. Contrary to surgical replacement of pulmonary valve (PVR), PPVI does not involve any incisions in the myocardium — a frequent cause of a conduction block and arrhythmias, which worsen heart function [19]. PPVI leading to restoration of pulmonary valve function, similarly to PVR, simultaneously being a less invasive method, could be expected to have a positive effect on heart function and consequently exercise performance. There is, however,

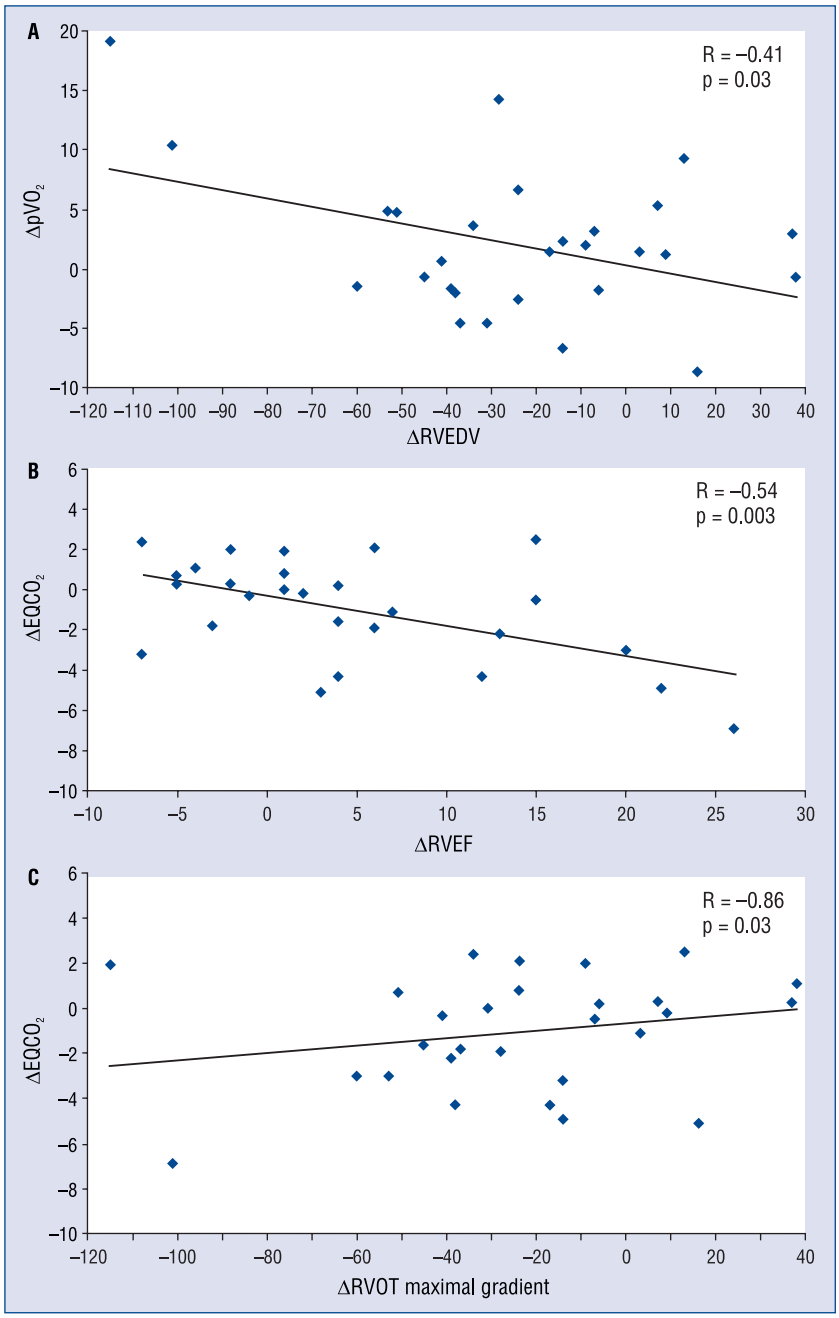

Figure 3. Results of peak oxygen uptake (pVO_2) and ventilatory equivalent for oxygen consumption ($EQCO_2$) before and 12 months after percutaneous pulmonary valve replacement (PPVI); Δ — indicates change (from baseline to 1 year post implantation); R — Pearson correlation coefficient; RVEDV — right ventricular end-diastolic volume; RVEF — right ventricular ejection fraction; RVOT — right ventricular outflow tract.

no clear evidence of improvement in cardiopulmonary function after the procedure [11, 15, 18, 20, 21]. In our study, a small but significant improvement in peak VO_2 and $EQCO_2$ were reported.

In order to understand the outcomes of the conducted experiments, patients' magnetic resonance imaging and TTE were investigated and then the findings were correlated with CPET data. An important finding derived from the study was that the improvement in RV function following RVOT gradient reduction due to PPVI, led to exercise function improvement (Fig. 3). Healthy subjects respond to exercise by increasing RV pressure and pulmonary blood flow [22]. In patients with RVOT dysfunction there is poor exercise performance resulting from (1) submaximal pulmonary circula-

tion, (2) pressure overload of RV. In line with this description and previous studies, we reported that in patients with congenital heart disease with pulmonary conduit dysfunction exercise capacity is significantly impaired [18, 23].

In terms of RV overload, patients with PR differ from patients with PS. PR leads to RV volume overload, observed as an increase in RVEDV that could be followed in our study. In patients with PS, however, abnormal loading conditions lead to an increase in RVESV with no change in RVEDV. In this group, PPVI leads to reduction in RVESV, with no change in RVEDV. The results are consistent with the findings by Coats et al. [11, 20].

Releasing RV from volume and pressure overload due to PPVI combined with increased RVEF might be assigned to a better pulmonary arterioles blood flow. Consequently, increased pre-load improves LVEF. The relocation of blood towards pulmonary circulation enhances the blood saturation, which combined with an increase in biventricular effective stroke volume, results in improved physical capacity (examined by change in peak VO_2 and ventilatory equivalent for CO_2). Also, the subjective component, reflected by the duration of workload in CPET and NYHA classification, clearly indicated an improvement in cardiopulmonary function. These findings are consistent with previous studies examining the correlation between changes in RV and LV functions and exercise capacity. Lurz et al. [4] described post-procedural improvement in peak oxygen uptake and minute ventilation/carbon dioxide elimination slope as a result of RV and LV effective stroke volume increase during exercise in patients with PS, which is consistent with our findings.

Our data suggest a clear positive influence of PPVI on peak VO_2 and a link between peak VO_2 and magnetic resonance imaging parameters connected with the right heart physiology. In our study, however, we observed a significant but small improvement in peak VO_2. The cause of that might be a considerably small group of patients included in the study and different factors affecting peak VO_2, such as: oxygen carrying capacity of the blood, peripheral blood flow, extraction by the tissue, pulmonary diseases, quantity of exercising muscles, fat-free mass. Another limitation of using peak VO_2 in assessing exercise performance is the inaccuracy of measuring external work rate when performing a treadmill test. Peak VO_2 is acknowledged as a gold standard for cardiorespiratory fitness. In clinical testing, however, we should make allowances for symptom limitation of exercise, which is often the case in patients with congenital heart disease.

An improvement in medical databases is typically defined with regard to standards. In the case of patients with congenital heart disease, however, the physiology of the heart differs from that in other individuals, moreover it changes during exercise. That is why acknowledging the indicators of "improvement" is not simple. In the case of patients with pulmonary regurgitation, we observed post-procedural reduction in RVEDV as a result of reduced blood retrograde flow through the pulmonary valve during diastole. That supports the findings by Coats et al. [11], who explained that RV in this group of patients is on decompensatory limb of the Starling curve at baseline which shifts leftwards back to the compensatory limb following PPVI. The group of patients with predominant stenosis show a different pattern of RV hemodynamics following the procedure. The decompensated state, contrary to what is seen in PR group, is a result of increased afterload. Intervention relieves abnormal loading conditions and consequently decreases RVESV. These findings are similar to the results reported by Coats et al. [20].

In order to describe "improvement" in all patients, independently of the type of dominant lesion, we chose to use CPET parameters, considering the fact that impaired physical capacity is reported to be the one of the first signs of decline in RV function in asymptomatic patients [5]. The improvement was assessed using: (1) peak VO_2 — an important parameter defining the limits of the cardiopulmonary system [24]; (2) ventilatory response to exercise, defined as $EQCO_2$ (VE/VCO_2) at maximally obtained duration of exercise in both tests before and after PPVI. Both elements of the $EQCO_2$ formula change with the duration of the exercise, which encouraged us to include the results at the same time point.

Limitations of the study

The main limitation of the study was a small group of patients. It is possible that increasing the study population might help find the factors associated with the post-procedural improvement. Additionally, the follow-up period was rather short so we were unable to comment on a long-outcome of the procedure (over 1 year). The mean respiratory exchange ratio was 0.98, which indicated that in some patients, the physical effort was submaximal, consequently their results might have been underestimated.

The Wasserman standard formula, used for calculating predicted peak VO_2 is valid for patients aged over 20 years. Five out of 29 patients included in the study were under the age of 20 years, which

made us use peak VO_2 instead of predicted peak VO_2 for further calculations.

Conclusions

The results directed us to three major conclusions: (1) PPVI resulted in an improvement in the duration of workload, peak oxygen uptake and $EQCO_2$. (2) Ventilatory equivalent for CO_2 and peak VO_2 were convenient for the assessment of post-procedural improvement. (3) The correlation between an improvement in $EQCO_2$ or peak VO_2 and baseline characteristics was too weak to reliably identify the group of patients that will benefit from the procedure.

Conflict of interest: Marcin Demkow — personal fees from Medtronic; other authors — no conflict of interests reported.

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