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Impact of percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction on exercise recovery kinetics

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ABSTRACT

The recovery of cardiopulmonary variables from peak exercise in patients with pulmonary stenosis (PS) or regurgitation (PR) is delayed, but the impact of treating PS or PR on exercise recovery kinetics is unknown.

43 patients (median age 14 years) with PS ($n = 23$) or PR ($n = 20$) after repair of congenital heart disease underwent successful percutaneous pulmonary valve implantation (PPVI). Cardiopulmonary exercise tests (CPET) were performed both before and within 1 month after PPVI. Apart from peak oxygen uptake (VO_2), the constant decay of VO_2, CO_2 output (VCO_2), minute ventilation (VE), and heart rate (HR) and oxygen pulse were calculated for the first minute of recovery as the first-degree slope of a single linear relation.

PPVI led to a significant improvement in NYHA functional class in the PS and PR groups ($p < 0.001$ and $p = 0.0015$, respectively). On CPET, peak VO_2 improved post-PPVI only in the PS (25.6 ± 6.2 vs. 27.8 ± 7.9 ml/kg/min; $p = 0.01$) but not PR group (29.0 ± 9.8 vs. 28.6 ± 8.9 ml/kg/min; $p = 0.6$). However, VO_2 slope improved in the PS (0.40 ± 0.23 vs. 0.65 ± 0.27, $p < 0.001$) as well as in the PR group (0.56 ± 0.37 vs. 0.67 ± 0.37, $p = 0.003$) as did VCO_2 slope (0.39 ± 0.2 vs. 0.55 ± 0.24, $p = 0.002$ and 0.42 ± 0.33 vs. 0.53 ± 0.35, $p = 0.02$: for the PS and PR groups, respectively). The VE and HR slopes did not change after PPVI.

Despite the lack of improvement in exercise capacity in the PR group, treatment of PS and PR by PPVI induces significant and similar improvements in the ability of recovering from maximal exercise in the 2 groups.

1. Introduction

Percutaneous pulmonary valve implantation (PPVI) has been proven to be a safe and effective treatment for right ventricular outflow tract (RVOT) dysfunction in patients with congenital heart disease [1–5]. This non-surgical therapy leads to a significant reduction in RVOT obstruction and pulmonary regurgitation (PR) [1–5]. Consequently, several studies demonstrated a marked symptomatic improvement following PPVI, observed in both patients with predominantly pulmonary stenosis (PS) and in patients with predominantly PR [1–7]. However, although maximal cardiopulmonary exercise capacity as described by peak oxygen uptake (peak VO_2) improves in patients treated for PS, there is no improvement in exercise capacity in patients with PR [6,8,9]. Hence, there is clear discrepancy in the response of objective parameters of maximal cardiopulmonary exercise capacity and patients' subjective symptoms.

Even though peak VO_2 has been identified as a powerful predictor of mortality and morbidity in these patients with congenital heart disease [10,11], it remains unclear, how well peak VO_2 is able to predict how patients will ultimately do during their daily activity routines. Apart from peak exercise performance, the ability to recover quickly from exercise might also impact on patients' symptoms and subjective exercise tolerance [12]. Although severe PR is known to cause impaired recovery from exercise in patients with tetralogy of Fallot [13], the potential reversibility of this finding after RVOT interventions remains unknown.

The aim of this study was to assess the impact of PPVI on the ability to recover from maximal exercise in patients with RVOT dysfunction. A better understanding of changes in exercise physiology occurring after PPVI should add to the way we judge procedural success of RVOT interventions at present.

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2. Methods

2.1. Patients and study protocol

In this prospective study, 43 consecutive patients fulfilling the inclusion criteria were recruited. Patients were recruited at two different implantation sites (Great Ormond Street Hospital for Children, London, UK; Heart Center of the University of Leipzig, Leipzig, Germany). Patients were included if they had either a predominantly stenotic lesion prior to treatment (defined by a gradient across the RVOT > 50 mm Hg on echocardiography and < 25% pulmonary regurgitation fraction on MRI; PS group) or a predominantly regurgitant lesion (defined by a gradient across the RVOT < 50 mm Hg on echocardiography and > 25% pulmonary regurgitation fraction on MRI; PR group). Patients also had to fulfil morphological criteria for PPVI, as published previously [1,14]. Patients who presented with mixed RVOT lesions (who did not fulfil criteria either for a predominantly stenotic lesion or for a predominantly stenotic lesion) were excluded. Other exclusion criteria were contraindication for MR imaging or exercise testing.

Valve implantation was performed under general anaesthesia. Pressure measurements were carried out before and immediately after PPVI as previously reported [1,8]. Patients were classified into NYHA functional class pre- and post-PPVI.

Written informed consent was obtained from patients and parents as appropriate. The ethics committees at the two contributing Institutions approved the study protocol.

2.2. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed on a bicycle ergometer before PPVI and at a median of 4 days (range 3 to 42 days) after PPVI. Work rate was increased with a ramp protocol. A 12-lead ECG was monitored continuously and blood pressure recorded every 2 min during exercise. Breath-by-breath respiratory gas exchange measurements were recorded throughout the test and averaged over a peak width of 20 s at the end of exercise to determine maximum values. Patients were encouraged to exercise until exhaustion. Only maximal tests (defined by a respiratory exchange ratio of ≥1.09) were included into data analyses. The constant decay of VO_2, carbon dioxide production (VCO_2), minute ventilation (VE), oxygen pulse slope and heart rate expressed as the first-degree slope of a single linear relation were calculated for the first minute of recovery by means of linear regression (Fig. 1) [13,15,16]. The first minute was chosen to guarantee that the measurements reflected the alactic phase of the repayment of O_2 debt [12].

2.3. Magnetic resonance imaging

MRI was performed at 1.5 T (Symphony Maestro Series and Avanto; Siemens Medical Solutions, Erlangen, Germany and Gyroscan Intera CV, Philips Medical Systems, Best, The Netherlands). Retrospective gated steady-state free-precession cine magnetic resonance images of the heart were acquired in the vertical long-axis view, 4-chamber view, and short-axis view that included the extent of both ventricles (9 to 12 slices), and 2 long-axis planes of the RVOT for positioning of through-plane flow quantification.

Aortic and pulmonary artery flow data were acquired with a flow-sensitive gradient echo sequence during free breathing. The detailed imaging protocols for assessment of ventricular function and great vessel blood flow were described previously [8]. Regurgitant fraction was calculated as the percent backward flow over forward flow.

2.4. Statistical analysis

Data were tested for normal distribution by the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± SD, while not normally distributed data as median and interquartile range (IQR) or range. Proportions are expressed as number of patients and percentages. Changes from before to PPVI in the PS and PR groups were analysed with paired Student's t-test. Parameters pre-PPVI within the 2 groups were compared with un-paired Student's t-test. A Wilcoxon signed ranks test was used to assess the change in functional class before and after PPVI. Categorical variables were compared with the use of Fisher's exact test. Pearson correlation analyses were performed to study the relationship between peak VO_2 and the VO_2 recovery slope before and after PPVI.

All statistical tests were two-sided and a p-value of < 0.05 was considered statistically significant. Statistical testing and data analysis were performed with Prism version 5.0b for Mac OS X (GraphPad Software Inc., SPSS Inc., La Jolla, CA, USA).

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. The median age of the patient population was 14 years (IQR 12–17); 40% were female. Most patients (65%) had tetralogy of Fallot or a variant morphology; 77% of patients had a pulmonary homograft placed at previous surgery. Homografts were more frequent in the PS group as compared to the PR group (96% vs. 55%, p = 0.003). Other baseline characteristics including age, sex, diagnosis, and NYHA functional class did not differ significantly in the PS and PR groups.

Groups were significantly different for echocardiographically determined RVOT gradient (78.1 ± 18.8 vs. 33.2 ± 9.8 mm Hg; p < 0.001), PR fraction (8.8 ± 6.4 vs. 39.2 ± 9.9%; < 0.001) and right ventricular end-diastolic diameter (102.3 ± 33.2 vs. 128.2 ± 42.2 ml/m^2; p < 0.039) as determined by MRI.

3.2. Haemodynamic result

Invasive pressure measurements are summarized in Table 2. According to the inclusion criteria and grouping of patients, patients in the PS group had significantly higher RV systolic pressure (69.4.6 ± 14.7 vs. 45.9 ± 37.5 mm Hg; p < 0.001 compared to the PR group) and RVOT gradient (48.1 ± 16.8 vs. 17.5 ± 11.9 mm Hg; p < 0.001) pre-PPVI.

PPVI resulted in a significant reduction in RV systolic pressure and pulmonary artery to RV pullback gradient. Whereas end-diastolic pressure decreased in both groups, this was significant only in the PR group. Systolic aortic pressure increased in both groups post-PPVI.

3.3. Functional outcome

PPVI led to a significant improvement in NYHA functional class in both groups (patients in functional class I 17.3 vs. 82.6% and 20 vs. 65% pre- vs. post-PPVI in the PS and PR groups respectively; p < 0.001 and p = 0.0015; Fig. 2).

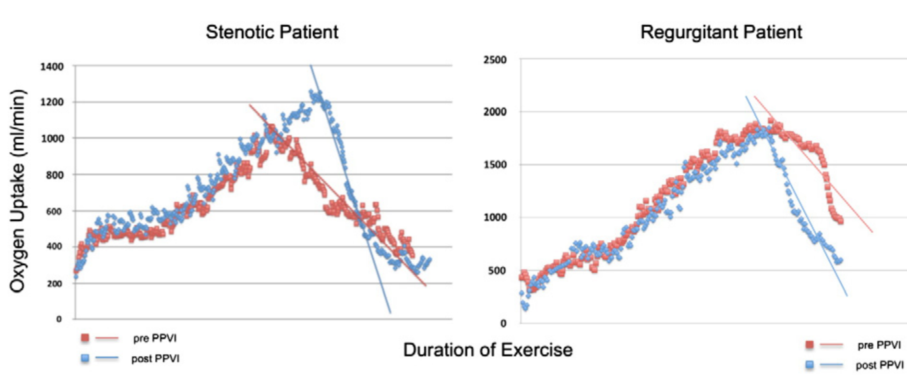

Fig. 1. Oxygen uptake kinetics during exercise and recovery. Oxygen uptake kinetics during exercise and recovery in a patient with predominantly pulmonary stenosis prior to PPVI (red) and after PPVI (blue). Note the increased peak oxygen uptake after intervention, which was also accompanied by a steeper decay in oxygen uptake during recovery. Right panel: Oxygen uptake during exercise and recovery in a patient with predominantly pulmonary regurgitation prior to PPVI (red) and after PPVI (blue). Whereas peak oxygen uptake after intervention remained unchanged, there was a marked steeper decay in oxygen uptake during recovery, suggesting an improved recovery from exercise after PPVI in this patient.