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Early Versus Late Functional Outcome After Successful Percutaneous Pulmonary Valve Implantation

Are the Acute Effects of Altered Right Ventricular Loading All We Can Expect?

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Objectives The purpose of this study was to assess the potential of late positive functional remodeling after percutaneous pulmonary valve implantation (PPVI) in right ventricular outflow tract dysfunction.

Background PPVI has been shown to impact acutely on biventricular function and exercise performance, but the potential for further late functional remodeling remains unknown.

Methods Sixty-five patients with sustained hemodynamic effects of PPVI at 1 year were included. Patients were divided into 2 subgroups based on pre-procedural predominant pulmonary stenosis (PS) (n = 35) or predominant pulmonary regurgitation (PR) (n = 30). Data from magnetic resonance imaging and cardiopulmonary exercise testing were compared at 3 time points: before PPVI, within 1 month (early) and at 12 months (late) after PPVI.

Results There was a significant decrease in right ventricle end-diastolic volume early after PPVI in both subgroups of patients. Right ventricle ejection fraction improved early only in the PS group (51 ± 11% vs. 58 ± 11% and 51 ± 12% vs. 50 ± 11%, $p < 0.001$ for PS, $p = 0.13$ for PR). Late after intervention, there were no further changes in magnetic resonance parameters in either group (right ventricle ejection fraction, 58 ± 11% in the PS group and 52 ± 11% in the PR group, $p = 1.00$ and $p = 0.13$, respectively). In the PS group at cardiopulmonary exercise testing, there was a significant improvement in peak oxygen uptake early (24 ± 8 ml/kg/min vs. 27 ± 9 ml/kg/min, $p = 0.008$), with no further significant change late (27 ± 9 ml/kg/min, $p = 1.00$). In the PR group, no significant changes in peak oxygen uptake from early to late could be demonstrated (25 ± 8 ml/kg/min vs. 25 ± 8 ml/kg/min vs. 26 ± 9 ml/kg/min, $p = 0.48$).

Conclusions In patients with a sustained hemodynamic result 1 year after PPVI, a prolonged phase of maintained cardiac function is observed. However, there is no evidence for further positive functional remodeling beyond the acute effects of PPVI. (J Am Coll Cardiol 2011;57:724–31) © 2011 by the American College of Cardiology Foundation

The acute physiological responses to percutaneous pulmonary valve implantation (PPVI) are different in patients with predominant right ventricular outflow tract (RVOT) obstruction compared with those with significant pulmonary regurgitation (PR). After reduction of RV afterload, patients showed an immediate improvement in right ventricle (RV) function and maximal exercise capacity (1–3); however, this is not seen in patients after restoration of PR (3,4). Data on late physiological outcome after percutaneous restoration of RVOT function are scarce. It is unknown whether percutaneous restoration of RVOT function can promote cardiac remodeling beyond the early period after

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intervention, thus improving cardiac function and exercise capacity in the midterm, or whether it simply interrupts the downward spiral of worsening cardiac function, leading to a stabilization of biventricular performance and exercise tolerance.

The aim of this study was to analyze the immediate and 1-year physiological responses to PPVI. In particular, we sought to analyze whether further changes in biventricular function and exercise performance (functional remodeling) occurred after the immediate post-interventional period. For this purpose, we enrolled patients into a prospective study protocol that included magnetic resonance (MR) imaging and cardiopulmonary exercise (CPEX) testing. To avoid a significant confounding effect of restenosis or occurrence of PR, only patients with a sustained hemodynamic result 1 year after PPVI were included in this study.

Methods

Patients and study protocol. To assess the acute and late effects of PPVI on biventricular function and exercise performance, MR imaging and CPEX testing were performed at 3 time points: first, within 1 month before PPVI (before PPVI); second, within 1 month after PPVI (early after PPVI); and third, 12 months after PPVI (late after PPVI).

Patients underwent PPVI according to the clinical and morphological criteria that have been published previously (5–7) and were enrolled in this study from May 2004 through June 2008. For initial inclusion into the study, patients had to fulfill the following criteria: no contraindications to MR imaging or CPEX testing, adequate MR image quality for assessment of ventricular volumes and great vessel blood flow, and symptom-limited maximal CPEX results with a respiratory exchange ratio ≥1.09. To avoid confounding of the data related to nonsustained efficacy of the procedure, patients had to show a sustained hemodynamic result 1 year after PPVI as assessed by echocardiography (no increase in peak RVOT gradient >15 mm Hg and no increase in PR). Only patients with a complete MR imaging and CPEX testing data set at all 3 assessment stages were analyzed. In total, 65 of 107 screened patients met these inclusion criteria. Figure 1 summarizes reasons for exclusion from the study.

Patients were divided into 2 groups according to PR fraction measured on MR imaging to separate patients with predominant pulmonary stenosis (PR fraction ≤25%, n = 35) from those with predominant PR (PR fraction >25%, n = 30). The New York Heart Association (NYHA) functional class was assessed at the same clinical contacts in all patients.

Written informed consent was obtained from patients and parents as appropriate. The ethics committees at the 2 contributing institutions approved the study protocol (Great Ormond Street Hospital for Children and The Heart Hospital, London, United Kingdom).

PPVI. The protocol for valve implantation (Melody, Medtronic, Inc., Minneapolis, Minnesota) has been reported before (5,8–10) and is summarized here briefly for convenience. All implants were performed under general anesthesia. Vascular access was achieved through the femoral vein and artery. Standard right heart catheterization, including pressure measurements and RVOT angiography, was undertaken. Invasive systemic pressures were monitored. Aortic root angiography was performed routinely to assess the proximity of the coronary arteries to the RVOT to avoid possible coronary compression resulting from PPVI. Simultaneous balloon inflation in the RVOT and coronary angiography was performed in patients at risk for coronary obstruction (5,11–13). Very stenotic, tortuous conduits were pre-dilated with high-pressure Mullins balloons (NuMed, Hopkinton, New York) or pre-stented with IntraStent Max LD stents (ev3 Intravascular, Plymouth, Minnesota). After PPVI, pressure measurements and RVOT angiography were performed. Post-dilatation with high-pressure Mullins balloons was performed after PPVI where appropriate.

Abbreviations and Acronyms

CPEX = cardiopulmonary exercise
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
MR = magnetic resonance
NYHA = New York Heart Association
PPVI = percutaneous pulmonary valve implantation
PR = pulmonary regurgitation
PS = pulmonary stenosis
RV = right ventricle
RVOT = right ventricular outflow tract

Echocardiography. All transthoracic echocardiographic studies were performed on a Vivid 7 GE machine (Vingmed, Milwaukee, Wisconsin). As an estimate of RV systolic pressure, the RV-to-right atrium pressure gradient was calculated from the tricuspid regurgitant jet (without addition of right atrial pressure). The peak RVOT gradient was calculated from the continuous-wave Doppler velocity across the RVOT (14). PR was defined qualitatively by color flow Doppler (15).

CPEX testing. CPEX testing was performed on a bicycle ergometer. The work rate increased with a ramp protocol of 10 to 20 W/min to reach exhaustion after approximately 10 min of exercise. Tests were considered to be maximal when they were interrupted because of symptoms like fatigue or dyspnea and a respiratory exchange ratio ≥1.09 was achieved. A 12-lead electrocardiography test was monitored continuously and blood pressures were recorded every 2 min during CPEX testing. Breath-by-breath respiratory gas exchange measurements were recorded throughout the test. Peak oxygen uptake was defined as the average of the values obtained in the last 20 s of exercise. Anaerobic threshold was determined by the modified V-slope method (16). Ventilatory efficiency, defined as the slope between minute ventilation and carbon dioxide elimination (ventilatory efficiency slope, or VE/VCO_2 slope) was obtained by linear

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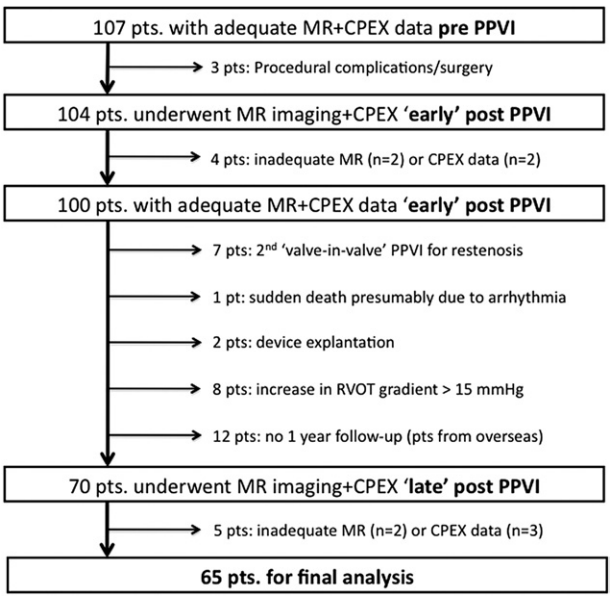

Figure 1 **Summary of Study Enrollment and Reasons for Exclusion**

Initial inclusion criteria (no contraindication to magnetic resonance [MR] imaging and cardiopulmonary exercise [CPEX] testing; adequate MR and CPX data before percutaneous pulmonary valve implantation [PPVI]) were met by 107 patients after intervention; 3 patients did not undergo assessment early after PPVI because of procedural complications and rescue open-heart surgery. Of the 104 patients undergoing assessment early after PPVI, 4 were excluded because of inadequate MR data (n = 2) and submaximal CPEX testing (n = 2). During follow-up, 30 patients were excluded from the study because of: second valve-in-valve PPVI for early restenosis (n = 2), sudden death presumably resulting from arrhythmia (n = 1), device explantation resulting from endocarditis (n = 1) and mechanical aortic valve failure (n = 1); relevant restenosis as defined by an increase in right ventricular outflow tract (RVOT) gradient >15 mm Hg as assessed on echocardiography (n = 8); and missed assessment late after PPVI in overseas patients (n = 12). Finally, of 70 patients who underwent assessment late after PPVI, 5 were excluded because of inadequate MR data (n = 2) and submaximal CPEX testing (n = 3), leaving 65 patients for final analysis.

regression analysis using breath-to-breath data acquired throughout the exercise period (17).

MR imaging. MR imaging was performed at 1.5-T (Symphony Maestro Series and Avanto, Siemens Medical Solutions, Erlangen, Germany). Retrospective gated steady-state free-precession cine MR images of the heart were acquired in the vertical long-axis view, 4-chamber view, short-axis views that included the entirety of both ventricles (9 to 12 slices), and 2 long-axis planes of the RVOT and left ventricular outflow tract for positioning of through-plane flow quantification. Assessment of RV and left ventricular volumes was performed by manually defining the endocardial outline at end-diastole and end-systole in each of the short-axis cine images (Argus, Siemens Medical Systems, Erlangen, Germany). The end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated with Simpson's rule for each ventricle, and from these volumes, the stroke volume and ejection fraction (EF) were derived. The cine steady-state free-precession sequence parameters were as follows: repetition time, 2.4 ms; echo time, 1.1 ms; flip angle, 60°; slice thickness, 8 to 10 mm (no gap in short-axis stack); matrix size, 192 × 156; and field of view, 280 to 380 mm, with a temporal resolution of approximately 40 ms reconstructed to 25 phases per cardiac cycle.

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 biventricular function and great vessel blood flow were described previously (1). The flow sensitive gradient echo sequence parameters were as follows: repetition time, 8 ms; echo time, 3.8 ms; flip angle 30°; slice thickness, 5 mm; matrix size 256 × 192; and field of view, 280 to 380 mm, with a temporal resolution of approximately 30 ms reconstructed to 30 phases per cardiac cycle.

Regurgitant fraction was calculated as the percent of backward flow over forward flow. Where PR was present, an effective RV stroke volume was calculated to reflect the net forward blood flow into the pulmonary arteries as follows: effective RV stroke volume = total pulmonary artery forward flow − pulmonary artery backward flow. Tricuspid regurgitation fraction was calculated as follows: total RV stroke volume − total pulmonary artery forward flow. All volume and flow measurements were indexed for body surface area and expressed in milliliters per square meter.

Statistical analysis. Data are expressed as mean ± SD. Proportions are expressed as percentages. Two-paired samples were analyzed with a 2-tailed paired Student *t* test. Parameters before PPVI were compared between the 2 groups with the unpaired Student *t* test or Mann-Whitney *U* test. Categorical variables were compared using the Fisher exact test. MR imaging, CPEX testing, and echocardiographic data were compared with repeated-measures analysis of variance and post-hoc testing with Bonferroni correction between the states early after PPVI and late after PPVI. For comparison of NYHA functional class, a Friedman test was applied for comparison between the 3 points in time within the same subgroups. All statistical testing was based on a 2-sided $\alpha = 0.05$ significance level. Statistical testing and data analysis was performed with SPSS software version 11 (SPSS, Inc., Chicago, Illinois) and GraphPad Prism software version 5.0b (GraphPad Software, San Diego, California).

Results

Patient characteristics are shown in Table 1. The median age at the time of PPVI was 20.4 years (range 5.2 to 57.7 years), and 38.5% of the patients were female. Most patients (63.1%) had tetralogy of Fallot or variant morphology. Fifty-nine of 65 patients (90.7%) had an RV-to-PA conduit in situ, 5 patients had a native or patch-extended RVOT at presentation, and 1 patient had a bioprosthetic valve in pulmonary position. Baseline characteristics, including age,

Table 1 Baseline Characteristics

Parameter	Total Population (n = 65)	PS Group (n = 35)	PR Group (n = 30)	PS Group vs. PR Group (p Value)
Age at implantation, yrs (range)	20.4 (5.2–57.7)	22.0 (7.0–44.1)	19.8 (5.2–57.7)	0.15
Female	25 (38.5)	13 (37.1)	12 (40.0)	1.00
Diagnosis				
Tetralogy of Fallot variant	41 (63.1)	21 (60.0)	20 (66.7)	0.6
Double outlet right ventricle	3 (4.6)	1 (2.9)	2 (6.7)	1.00
TGA, VSD, PS	7 (10.8)	5 (14.3)	2 (6.7)	0.44
Ross procedure	5 (7.7)	3 (8.6)	2 (6.7)	1.00
Truncus arteriosus	6 (9.2)	2 (5.7)	4 (13.3)	0.40
Other	3 (4.6)	3 (8.6)	0	0.24
Open heart surgeries (mean)	2 (1–5)	2.0 (1–5)	1 (1–5)	0.08
Closed heart surgeries (mean)	0 (0–3)	0 (0–2)	0 (0–3)	0.40
Operations in total (mean)	2 (1–6)	2 (1–6)	2 (1–6)	0.37
NYHA functional class				
I	10 (15.4)	7 (19.0)	3 (10.0)	0.32
II	39 (60.0)	18 (51.4)	21 (70.0)	0.20
III	15 (23.1)	9 (25.7)	6 (20.0)	0.77
IV	1 (1.5)	1 (2.9)	0 (0)	1.00

Values are n (%) unless otherwise specified.
NYHA = New York Heart Association; PR = pulmonary regurgitation; PS = pulmonary stenosis; TGA = transposition of the great arteries; VSD = ventricular septal defect.

sex, diagnosis, and NYHA functional class, did not differ significantly between the PS and the PR groups.

Acute hemodynamic outcome. Invasive pressure measurements are summarized in Table 2. PPVI resulted in a significant reduction in RV systolic pressure, pulmonary artery-to-RV pullback gradient, and RV end-diastolic pressure in both groups. Further, PPVI led to an increase in systemic systolic pressure in the PS group (93 ± 15 mm Hg vs. 102 ± 14 mm Hg, p = 0.004) and PR group (89 ± 13 mm Hg vs. 103 ± 18 mm Hg, p < 0.001).

Echocardiography. Before PPVI, there were significantly higher echocardiographic RVOT gradients in the PS group compared with the PR group (70 ± 17 mm Hg vs. 41 ± 18 mm Hg, p < 0.001). Early after PPVI, the RVOT gradients fell significantly in the PS group (70 ± 17 mm Hg vs. 35 ± 10 mm Hg, p < 0.001, post-hoc testing before PPVI vs. early after PPVI) and in the PR group (41 ± 18 mm Hg vs. 27 ± 11 mm Hg, p = 0.001). Although this gradient reduction remained unchanged at 1 year in the PR group (27 ± 11 mm Hg vs. 26 ± 12 mm Hg; p = 1.00, post-hoc testing early after PPVI vs. late after PPVI), there was a further small reduction in RVOT gradient in the PS group (35 ± 10 mm Hg vs. 29 ± 10 mm Hg, p = 0.008).

MR imaging assessment and ventricular volumes and function. Volumetric assessment of the RV and calculation of pulmonary artery blood flow showed an improvement in effective RV stroke volume early after PPVI in both the PS and the PR group (Table 3). However, although RV EDV and ESV decreased significantly early after PPVI in both groups, RV EF improved only in the PS group with no change in the PR group. PR fraction was reduced to a minimum early after PPVI in both groups. There was a significant increase in left ventricular EDV and effective stroke volume in the PS and PR group early after intervention.

On MR assessment late after PPVI, the initial improvement in RV EF in the PS group was maintained with no further change compared with early after PPVI (Fig. 2). Also, there was no further reduction in RV EDV from early to late after PPVI in this group. Volumetric assessment of the LV in the PS group showed a slight, but significant, increase in EDV and ESV late after PPVI with unchanged

Table 2 Invasively Measured Hemodynamic Outcomes After Percutaneous Pulmonary Valve Implantation

	Stenotic Group (n = 35)			Regurgitant Group (n = 30)		
	Before	After	p Value	Before	After	p Value
RV systolic pressure (mm Hg)	71 ± 23	41 ± 10	<0.001	51 ± 16	39 ± 10	<0.001
RV end-diastolic pressure (mm Hg)	13 ± 5	10 ± 4	<0.001	11 ± 4	9 ± 3	0.02
RVOT gradient (mm Hg)	45 ± 23	15 ± 6	<0.001	22 ± 12	12 ± 7	<0.001
Aortic systolic pressure (mm Hg)	93 ± 15	102 ± 14	0.004	89 ± 13	103 ± 18	<0.001
Aortic diastolic pressure (mm Hg)	57 ± 11	61 ± 9	0.17	54 ± 11	61 ± 11.6	0.009
RV-to-systemic pressure ratio (%)	0.74 ± 0.16	0.40 ± 0.08	<0.001	0.57 ± 0.19	0.37 ± 0.09	<0.001

Values are mean ± SD.
RV = right ventricle; RVOT = right ventricular outflow tract.

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Table 3 Magnetic Resonance Imaging Data Before, Early After, and Late After PPVI in the Pulmonary Stenosis and Pulmonary Regurgitation Groups

Parameter	Before PPVI	Early After PPVI	Late After PPVI	p Value (ANOVA)	Post-Hoc Analysis: Before vs. Early	Post-Hoc Analysis: Early vs. Late
Predominantly stenotic (n = 35)						
RV EDV indexed (ml/m^2)	97.4 ± 30.4	86.9 ± 26.3	85.9 ± 20.3	<0.001	0.001	1.00
RV ESV indexed (ml/m^2)	50.9 ± 26.3	40.6 ± 23.8	38.2 ± 17.5	<0.001	<0.001	0.90
RV SV indexed (ml/m^2)	46.4 ± 9.1	47.2 ± 7.1	47.8 ± 7.7	0.70		
RV SV eff indexed (ml/m^2)	38.8 ± 7.9	45.1 ± 7.5	45.7 ± 8.0	<0.001	<0.001	1.00
RV EF (%)	50.7 ± 10.7	57.7 ± 10.5	57.8 ± 10.5	<0.001	<0.001	1.00
PR fraction (%)	11.4 ± 8.6	1.4 ± 2.6	1.9 ± 3.5	<0.001	<0.001	1.00
LV EDV indexed (ml/m^2)	68.7 ± 14.3	73.9 ± 13.9	77.5 ± 14.2	<0.001	0.002	0.04
LV ESV indexed (ml/m^2)	27.1 ± 12.0	27.0 ± 10.9	30.1 ± 12.1	0.008	1.00	0.03
LV SV eff indexed (ml/m^2)	39.9 ± 7.7	46.1 ± 6.5	46.2 ± 7.5	<0.001	<0.001	1.00
LV EF (%)	62.3 ± 9.6	64.6 ± 8.0	62.3 ± 9.0	0.02	0.0441	0.10
Predominantly regurgitant (n = 30)						
RV EDV indexed (ml/m^2)	118.2 ± 32.3	101.1 ± 31.2	97.9 ± 30.9	<0.001	<0.001	0.60
RV ESV indexed (ml/m^2)	60.5 ± 31.0	53.9 ± 29.5	49.5 ± 29.5	<0.001	0.016	0.145
RV SV indexed (ml/m^2)	57.5 ± 13.4	47.4 ± 7.4	48.4 ± 9.1	<0.001	<0.001	1.00
RV SV eff indexed (ml/m^2)	34.9 ± 7.3	44.3 ± 6.5	46.1 ± 9.2	<0.001	<0.001	0.50
RV EF (%)	50.9 ± 11.9	49.5 ± 10.8	52.3 ± 11.2	0.127		
PR fraction (%)	35.0 ± 10.5	3.1 ± 4.9	2.0 ± 3.5	<0.001	<0.001	0.60
LV EDV indexed (ml/m^2)	69.7 ± 18.4	79.5 ± 18.1	82.3 ± 25.6	<0.001	<0.001	0.71
LV ESV indexed (ml/m^2)	30.9 ± 15.0	32.8 ± 15.8	35.2 ± 21.6	0.064		
LV SV eff indexed (ml/m^2)	37.2 ± 7.2	45.4 ± 6.5	46.3 ± 9.3	<0.001	<0.001	1.00
LV EF (%)	56.9 ± 10.7	60.1 ± 9.5	60.2 ± 10.9	0.037	0.11	1.00

ANOVA = analysis of variance; EDV = end-diastolic volume; EF = ejection fraction; eff = effective; ESV = end-systolic volume; PPVI = percutaneous pulmonary valve implantation; RV = right ventricle; SV = systolic volume; other abbreviation as in Table 1.

LV EF compared with early after PPVI. In the PR group, the MR findings were maintained with no significant change in any MR parameters late after PPVI as compared with early after PPVI (Fig. 2).

Before PPVI, there were no patients with severe tricuspid regurgitation. The median tricuspid regurgitation fraction was 0.0% (range 0% to 33%), with only 2 patients having a tricuspid regurgitation fraction >20% (24% and 33%).

CPEX testing. The results of CPEX testing are shown in Table 4. In the PS group, there was a significant improvement in absolute measures of peak and percent of predicted peak oxygen uptake, peak workload, oxygen uptake at anaerobic threshold, and ventilatory efficiency slope early after PPVI. This early improvement in cardiopulmonary exercise capacity was maintained late after PPVI, with no further change in any of these parameters compared with early after PPVI.

In the PR group, no improvement in peak oxygen uptake and percent of predicted peak oxygen uptake, peak workload, oxygen uptake at anaerobic threshold, or ventilatory efficiency slope could be demonstrated early after PPVI. On repeated assessment of exercise capacity late after PPVI, there was a significant increase in peak workload and ventilatory efficiency slope as compared with parameters before PPVI. No significant change in peak oxygen uptake, percent of predicted peak oxygen uptake, and oxygen uptake at anaerobic threshold was seen late after PPVI. Peak heart rate and respiratory exchange ratio did not change early or late after PPVI in either group.

Functional outcome (NYHA functional class). The functional class fell from a median of NYHA II to NYHA I early after PPVI (p = 0.001, Friedman test), with no further statistically significant change late after PPVI (NYHA I). For this categorical variable, 25% of patients were in NYHA class III or IV before PPVI, whereas 100% were in NYHA class I or II at 1 year. These improvements in functional class also were present when separate analyses for the PS or the PR groups were made.

Discussion

In this study, we showed that the beneficial physiological consequences of PPVI seen in the acute setting (1–3) are maintained at 1 year in those patients with preserved device function. However, although there was no worsening of biventricular function or exercise capacity after 1 year, we have no evidence that the process of RV remodeling and functional improvement extends beyond the 1-month period in this patient group, as shown by MR imaging and CPEX results.

Acute effects of relief of adverse RV loading conditions. The present results confirm our previous findings that PPVI in patients with predominant PS is associated with an early significant improvement in RV systolic function and exercise capacity (4). This observation is thought to be the result

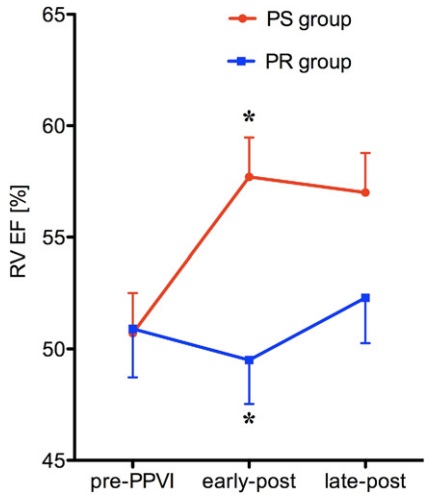

Figure 2 Change in RV EF as Assessed on MR Imaging

Initially, percutaneous pulmonary valve implantation (PPVI) led to a significant increase in right ventricular (RV) ejection fraction (EF) in the pulmonary stenosis (PS) group, whereas there was no significant change in the pulmonary regurgitation (PR) group. On late assessment 1 year after PPVI, no further changes in RV EF were seen, either in the PS group or in the PR group. *Significant change ($p < 0.05$) from before PPVI to early after PPVI.

of reduced RV pressure loading during exercise. This concurs with the experience of Jonsson et al. (18), who were able to demonstrate an association between RV systolic hypertension and reduced cardiac output response during exercise in patients with repaired tetralogy of Fallot, as a consequence of exercise-induced increases of RVOT pressure gradients. Under these conditions, significant RVOT obstruction limits the normal augmentation of cardiac output, which is elicited by exercise, thus reducing exercise capacity. Indeed, we recently were able to demonstrate that reduction in RVOT gradient was the only independent predictor of improved exercise capacity early after PPVI (4).

Conversely, in patients with predominant PR we observed no improvement in exercise capacity early after PPVI, despite a higher net flow to the pulmonary vasculature (increased effective RV SV) measured at rest. We postulate that the explanation for this finding is related to the fact that PR seems to be reduced to a minimum (both as percentage and as absolute value) at peak exercise and is not the limiting factor for cardiac output augmentation during exercise. This is likely to be related to shortening of diastole and reduced pulmonary vascular resistance during exercise (19). Therefore, by purely abolishing PR without improving RV ejection fraction, peak oxygen uptake may not be affected by PPVI acutely in this patient subgroup (4).

Late effects of relief of adverse RV loading conditions. Although acute functional changes after PPVI could be attributed to the load-dependent function of the RV (1,4,8) and to the consequences of ventricular interaction (2), a further remodeling of cardiac function and exercise capacity late after relief of adverse RV loading conditions could have been expected as a result of cardiac remodeling. However, although the early acute hemodynamic outcomes were well maintained at 1 year, we found no clear evidence for clinically relevant structural or functional improvement beyond the 1-month period in either subgroup.

On MR assessment in the PS group, there was no change in RV parameters late after PPVI as compared with early after PPVI. There was a significant increase in left ventricular EDV and ESV. We previously showed that the acute increase in left ventricular EDV is related to optimized ventricular interaction and increased filling of the left ventricle (2). The increase in left ventricular EDV 1 year

Table 4 Cardiopulmonary Exercise Testing Data Before, Early After, and Late After PPVI in the PS and PR Groups

Parameter	Before PPVI	Early After PPVI	Late After PPVI	p Value (ANOVA)	Post-Hoc Analysis: Before vs. Early	Post-Hoc Analysis: Early vs. Late
Predominantly stenotic (n = 35)						
% of predicted peak VO_2 (%)	59.9 ± 14.8	67.7 ± 17.3	68.9 ± 17.3	0.001	0.008	1
Peak VO_2 (ml/kg/min)	23.8 ± 7.9	26.8 ± 8.9	27.2 ± 8.8	0.001	0.008	1
VO_2 at AT (ml/kg)	14.5 ± 4.6	16.3 ± 5.7	16.4 ± 5.6	0.042	0.04	1
Peak work (Watts)	136.7 ± 52.5	147.7 ± 54.5	155.0 ± 57.1	0.013	0.23	0.61
VE/VCO_2 slope	34.8 ± 8.2	30.0 ± 6.2	29.9 ± 5.7	<0.001	<0.001	1
HR at peak exercise (beats/min)	166.8 ± 25.9	163.8 ± 24.0	164.0 ± 20.9	0.52	1	1
RER at peak exercise	1.18 ± 0.08	1.18 ± 0.08	1.2 ± 0.1	0.99	1	1
Predominantly regurgitant (n = 30)						
% of predicted peak VO_2 (%)	65.0 ± 16.4	66.9 ± 17.6	69.8 ± 19.8	0.036	0.41	0.52
Peak VO_2 (ml/kg/min)	24.8 ± 7.7	25.4 ± 7.6	26.1 ± 8.5	0.057	0.69	0.48
VO_2 at AT (ml/kg)	13.8 ± 5.9	14.1 ± 5.0	14.2 ± 6.2	0.43	1	1
Peak work (Watts)	108.3 ± 41.7	110.9 ± 42.0	123.7 ± 43.8	0.002	0.77	0.009
VE/VCO_2 slope	32.6 ± 6.1	31.1 ± 5.7	29.5 ± 5.0	0.001	0.24	0.051
HR at peak exercise (beats/min)	164.6 ± 22.4	161.3 ± 22.3	162.3 ± 19.8	0.58	1	1
RER at peak exercise	1.16 ± 0.05	1.16 ± 0.05	1.16 ± 0.06	0.6	1	1

AT = anaerobic threshold; HR = heart rate; RER = respiratory exchange ratio; VE/VCO_2 = ventilatory efficiency; VO_2 = oxygen uptake; other abbreviations as in Tables 1 and 3.

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after PPVI may be a reflection of late remodeling as a response to the acute improvement in filling over time; however, this cannot be answered in this study.

In the PR group, we found a nonsignificant tendency toward further reduction in RV EDV and improved RV EF 1 year after PPVI. Further studies have to clarify whether these changes can be attributed to late RV remodeling. Similar to the MR data, there was a tendency toward improved peak oxygen uptake and ventilatory efficiency on CPEX testing, but these subtle changes are unlikely to be of clinical relevance. Further, we found a significant increase in peak workload in the PR group. However, this finding is difficult to interpret as a follow-up parameter in growing children, because the studied parameter is not indexed for body weight. Assessment of patients' functional class revealed a further but nonsignificant reduction in the total number of patients in NYHA functional class II late after PPVI. Importantly, these 1-year results after PPVI predominantly for PR are in keeping with studies on surgical pulmonary valve replacement for PR, in which no significant improvement in peak oxygen uptake 1 year after surgery could be demonstrated (20,21).

In our opinion, with the current technique and indications for PPVI, the acute changes after PPVI are maintained 1 year after the intervention. However, no further relevant positive RV remodeling or functional improvement is seen as compared with early after PPVI.

The following factors may have limited positive late remodeling in the present study:

1. The hemodynamic result achieved by PPVI might not have been sufficient to allow for positive remodeling. Because only patients with sustained hemodynamic results were included in this study, the initial hemodynamic improvement was well maintained in the PR group with even further reduction in RVOT gradients in the PS group over time. Although this certainly should have limited the confounding effects of worsening RV loading conditions over time, some degree of residual RVOT obstruction was present in most patients. This hemodynamic finding was present in the PS and also in the PR group, where the impact of even low-pressure gradients is unknown.
2. PPVI might have been performed too late. Previous studies in the surgical literature that assessed functional outcome after pulmonary valve replacement have suggested that patients with severe PR often may be treated too late (20,22). This conclusion is based on the lack of improvement in RV function after pulmonary valve replacement. Similarly, in our study we also did not observe improvement in RV EF or exercise performance in patients with predominant PR, either immediately after PPVI or at 1 year. However, it remains unknown whether earlier performance of PPVI in this subgroup of patients would have resulted in improved outcomes.
3. Patients might not have been followed up for long enough. Adverse RV remodeling in these chronically ill patients may be reversible only in the long term.
4. RVOT dysfunction and adverse RV loading conditions represent only one of many possible contributors to functional impairment in these patients. The deleterious effects of neonatal hypoxia and cyanosis, high pulmonary pressures, multiple cardiopulmonary bypasses with long ischemic time and transient inflammation, and ventricular scaring resulting from surgery—all seen in patients with CHD involving the RVOT—could be affected only mildly by improved RV loading conditions after PPVI. Although certainly multifactorial, the contribution of adverse RV loading on impaired functional outcome in these patients may be less relevant than commonly believed. Further studies have to clarify the role of pulmonary valve replacement in patients with RVOT dysfunction for long-term patient management and outcome.

Study limitations. Although we saw no significant remodeling in our patients at 1 year, our study period may be too short and remodeling may occur over longer periods of time. The outcome parameters used in this study represent only selected proxies. Hard end point, such as mortality or arrhythmia burden, which are rare in studies on patients with congenital heart disease for well-known reasons, are still missing when procedural success of RVOT interventions is assessed. Further, the true onset of RVOT dysfunction could not be determined for each individual patient; thus, the data set does not allow for definite conclusions about the timing of intervention. Finally, the relatively small sample size represents a limitation of this study. Therefore, the findings need to be confirmed in larger cohorts.

Conclusions

With the current technique and indications for PPVI, patients can benefit from a prolonged phase of maintained cardiac function; however, they cannot expect significant further improvement in biventricular function and objective exercise performance 1 year after intervention. These results underline the need for further studies to address the question of when to intervene and how to achieve optimal hemodynamic acute and long-term results after RVOT intervention. At present, we suggest an aggressive approach to any acute post-procedural residual RVOT gradient. Importantly, in patients with chronic volume overload, even small gradients may have significant detrimental effects on RV function.

In patients with predominant PS, despite the lack of further remodeling at 1 year, the initial marked improvement is encouraging. In contrast, we observed no improvement in RV systolic function or exercise capacity in the PR group, which may suggest that in patients with severe PR, interventions should be considered before reduction in RV function or deterioration in exercise performance are observed.

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Key Words: cardiopulmonary exercise testing ■ congenital heart disease ■ magnetic resonance imaging ■ percutaneous pulmonary valve implantation ■ right ventricular outflow tract dysfunction.