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Cardiopulmonary exercise function among patients undergoing transcatheter pulmonary valve implantation in the US Melody valve investigational trial

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Objectives We assessed the hypothesis that there is an improvement in clinical and physiologic parameters of cardiopulmonary exercise testing (CPET) after implantation of a transcatheter pulmonary valve (TPV).

Background Transcatheter pulmonary valve provides a new tool for treating conduit stenosis and regurgitation in patients with right ventricle (RV) to pulmonary artery conduit dysfunction.

Methods Patients who underwent a TPV placement between January 2007 and January 2010 (N = 150) were investigated with a standardized CPET protocol before and at 6 months after TPV placement. Cardiopulmonary exercise testing was performed on a mechanically braked cycle ergometer with respiratory gas exchange analysis.

Results Six months post TPV, small but statistically significant improvements were observed in the maximum workload (65.0% ± 18.8% to 68.3% ± 20.3% predicted, $P < .001$) and the ratio of minute ventilation to CO_2 production at the anaerobic threshold (30.8 ± 4.7 to 29.1 ± 4.1, $P < .001$). There was no significant change in peak oxygen consumption (VO_2). Patients with pre-TPV hemodynamics consistent with RV dysfunction and patients with a lower pre-TPV peak VO_2 tended to have the greatest improvement in peak VO_2. The correlation between TPV-related improvements in peak VO_2 and baseline clinical variables were weak, however, and these variables could not be used to reliably identify patients likely to have improved peak VO_2 after TPV.

Conclusion In patients with RV to pulmonary artery conduit dysfunction, TPV is associated with modest improvement in exercise capacity and gas exchange efficiency during exercise. (Am Heart J 2012;163:280-7.)

In patients with certain forms of congenital heart disease, surgical repair involves placement of a right ventricular (RV) outflow tract (RVOT) conduit. Right ventricular outflow tract conduits almost inevitably become dysfunctional over time, with obstruction and/or regurgitation that can contribute to deterioration of RV function. Right ventricular outflow tract obstruction and pulmonary regurgitation (PR) have been linked to progressive exercise intolerance, right side of the heart failure, ventricular arrhythmia, and sudden death.[1,2] Historically, surgical pulmonary valve replacement has been the primary treatment option for patients with severe RVOT conduit dysfunction. Transcatheter pulmonary valve (TPV) placement is a recent development that has been reported to provide a safe and effective nonsurgical alternative for the treatment of RVOT dysfunction in this patient population.[3-5] As TPV therapy becomes more widely adopted, it is important to assess the clinical and physiologic consequences of the procedure objectively and quantitatively. The hemodynamic benefits of TPV implantation have been previously reported.[6-10] The purposes of this study were to characterize baseline cardiopulmonary exercise function and changes in exercise function after TPV with the Melody valve and to evaluate factors associated with improvement in exercise function among patients who underwent pre- and postimplant cardiopulmonary exercise testing (CPET) as part of the US Melody valve investigational device exemption (IDE) trial.

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Methods

The US Melody valve IDE trial is a nonrandomized, prospective, multicenter study of patients undergoing Melody valve implant for treatment of RVOT conduit dysfunction at 5 centers in the United States. Detailed inclusion and exclusion criteria as well as the evaluation and treatment protocols were summarized in prior reports.[6,11] Hemodynamic data were obtained during the catheterization, immediately before Melody valve implantation. Subjects underwent standardized CPET <2 months before TPV and then again at 6 months post TPV. The subjects also underwent echocardiographic and cardiac magnetic resonance imaging (MRI) studies at the implanting centers before and 6 months after implant. For each evaluation, data were recorded by the investigator and entered into an internet-based data collection system that is maintained by the sponsor of the trial, Medtronic Inc., Minneapolis, MN. Raw data from all echocardiograms, MRI studies, and exercise tests were forwarded to core laboratories that repeated all required measurements and entered them into the same internet-based data collection system. Core laboratory data were used for this study.

The study was conducted under an IDE (no. G050186), and all versions of and amendments to the protocol were approved by the Food and Drug Administration, the Center for Devices and Radiological Health, and the institutional review board at each institution. The trial is registered in ClinicalTrials.gov (identifier: NCT00740870).

Cardiopulmonary exercise testing protocol

A standard protocol was used at all participating centers. Baseline spirometric measurements were obtained in all patients. The patients then performed a maximal exercise test using a ramp protocol on an electronically braked cycle ergometer. Equipment was calibrated to manufacturers' specifications, and testing was performed with standard protocols previously used in subjects with congenital heart disease.[12]

Metabolic measurements

Expired gases were measured for 3 minutes of quiet rest and throughout the exercise protocol. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (V_E) were measured on a breath-by-breath basis. *Peak VO_2* was defined as the highest VO_2 achieved by the subject during the test. Ventilatory anaerobic threshold was measured by V-slope method when it could be accurately determined. Values for VO_2 were indexed to body weight and expressed as percentage of predicted values for healthy age- and gender-matched subjects as reported in previous studies with a similar protocol.[13,14] The ratio of V_E to VCO_2 (V_E/VCO_2 ratio) was measured at the ventilatory anaerobic threshold. The respiratory exchange ratio (RER; VCO_2/VO_2 ratio) was measured continuously. The O_2 pulse (VO_2/heart rate [HR]) was measured at peak VO_2. The O_2 pulse is equal to the product of forward stroke volume and the arterial-venous O_2 content difference. Because the arterial-venous O_2 content difference at peak exercise varies little among untrained subjects, the O_2 pulse may be used as a surrogate for forward stroke volume at peak exercise.[15] Arterial O_2 saturation was measured continuously with a pulse oximeter placed on the finger or ear.

To exclude data from patients who stopped exercising for noncardiovasclar reasons (ie, before approaching their cardiovascular limit), peak exercise data were excluded if the patient did not achieve an RER at peak exercise ≥1.05 or a HR at peak exercise ≥85% of predicted (in the absence of a tachyarrhythmia).

Table I. Demographic data (N = 150)

Age (y)		21.7 (7-53)
Weight (kg)		63.4 (27-147)
BMI		23.6 (14.1-41.1)
Gender (male)		96 (64%)
NYHA, class (%)	I	22 (15%)
	II	103 (69%)
	III	24 (16%)
	IV	1 (1%)
No. of surgeries		2.3 (1-6)

NYHA, New York Heart Association. Data are presented as mean (range) or n (%). *BMI*, body mass index.

Statistical analysis

Student paired *t* test was used to compare changes in indices of exercise performance from baseline to 6 months. The relationship between a continuous baseline variable and the primary outcome, the change in peak VO_2 (% predicted), was evaluated using Pearson correlation analysis. For categorical baseline variables including the primary indication categories (stenotic, regurgitant, and mixed) and tricuspid regurgitation (TR) severity (none/mild, moderate, or severe), changes from baseline to 6 months were compared within each subgroup using the paired *t* test, and changes from baseline to 6 months between subgroups were compared using unpaired 2-sample *t* test. In addition, multivariable linear regression analysis of factors associated with the change in % predicted peak VO_2 from baseline to 6 months post-TPV was performed using a forward stepwise model, with independent variables possessing $P < .05$ on univariable analysis entered into the model.

Patients were also divided into 2 groups based upon whether they had a clinically significant improvement in peak VO_2, which was defined as a ≥5 percentage point increase in peak VO_2 after TPV (eg, 60%-65% of predicted). The unpaired 2-sample *t* test was used to compare the baseline variables between groups. Receiver operator characteristic and contingency table analyses were then used to further assess the predictive power of the most promising baseline variable(s).

To adjust for multiple comparisons, we defined our level of significance at $P < .025$. Statistical software SAS 9.2 (Cary, NC) was used for all analyses.

The study was funded by Medtronic Inc. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Study population

A total of 150 subjects underwent TPV (Table I). Patients with a spectrum of RVOT conduit dysfunction were enrolled and evaluated in a systematic fashion. These included patients with tetralogy of Fallot (TOF), truncus arteriosus, aortic valve disease (Ross procedure),

Table II. Exercise and hemodynamic parameters before and after TPV implant

	n	Pre TPV	Post TPV	Difference	P
CPET					
Peak VO_2, mL/kg/min	98	25.0 ± 8.4 (25.5)	25.5 ± 7.6 (25.4)	0.5 ± 4.5	.28
Peak VO_2, % predicted	98	62.7 ± 18.7 (62.0)	64.7 ± 17.1 (64.6)	2.0 ± 11.4	.085
Oxygen pulse, % predicted	94	85.1 ± 21.8 (83.7)	87.5 ± 21.1 (87.5)	2.4 ± 14.3	.10
Work rate, W/kg	94	2.00 ± 0.60 (2.05)	2.07 ± 0.65 (1.98)	0.076 ± 0.29	.012
Work rate, % predicted	94	65.0 ± 18.8 (65.4)	68.3 ± 20.3 (68.4)	3.3 ± 9.3	.001
V_E/VCO_2 ratio at AT	105	30.8 ± 4.7 (30.0)	29.1 ± 4.1 (28.0)	−1.7 ± 3.3	<.0001
RER	98	1.12 ± 0.12 (1.14)	1.14 ± 0.11 (1.16)	0.02 ± 0.10	.098
Peak HR, beat/min	98	158.7 ± 21.9 (164.0)	159.0 ± 20.0 (158.5)	0.38 ± 14.3	.79
% Predicted FVC	114	76.4 ± 21.2 (76.5)	77.5 ± 21.1 (77.5)	1.1 ± 8.9	.19
% Predicted FEV_1	114	74.0 ± 21.0 (76.0)	75.3 ± 20.6 (77.0)	1.4 ± 9.0	.11
FEV_1/FVC	105	82.6 ± 9.8 (83.0)	83.0 ± 11.5 (84.0)	0.4 ± 12.6	.74
% Predicted peak expiratory flow rate	107	74.9 ± 25.1 (74.0)	76.8 ± 24.1 (77.0)	2.0 ± 16.2	.20
Echocardiography					
Doppler TR gradient	92	65.1 ± 18.1 (65.6)	45.2 ± 14.7 (41.0)	−19.9 ± 20.0	<.0001
RVOT gradient	105	55.6 ± 19.8 (57.8)	33.8 ± 12.9 (29.2)	−21.8 ± 19.4	<.0001
Cardiac MRI					
RVEDVI	76	126.5 ± 47.0 (112.2)	103.0 ± 36.4 (98.2)	−23.5 ± 20.7	<.0001
LVEDVI	76	81.0 ± 25.5 (76.5)	81.4 ± 21.3 (80.0)	0.4 ± 15.1	.82
RV/LVEDVI	77	1.6 ± 0.6 (1.6)	1.3 ± 0.4 (1.2)	−0.3 ± 0.4	<.0001
RVEF	77	43.2 ± 13.8 (43.8)	42.5 ± 12.2 (41.9)	−0.7 ± 12.5	.63
LVEF	77	55.5 ± 11.6 (56.9)	57.9 ± 9.9 (58.3)	2.4 ± 10.3	.047
PR fraction	76	23.8 ± 15.2 (25.6)	2.9 ± 3.2 (1.8)	−20.9 ± 23.4	<.0001

Data are presented as mean ± SD (median).
AT, Anaerobic threshold; *EF*, ejection fraction.

and transposition of the great arteries. Preimplant CPET was performed in 139 subjects (the remaining 11 subjects were unable to undergo CPET testing because of physical and cognitive limitations to performing the test), and 126 of these 139 subjects underwent repeat CPET 6 months postimplant (13 patients declined follow-up testing or were lost to follow-up). Of the 126 patients with pre- and postimplant studies, 98 met criteria for adequate effort (RER >1.05 or HR >85% predicted) on both studies.

Baseline exercise function

Before TPV, peak VO_2 was moderately depressed (62.7% ± 18.7% predicted) (Table II). A low baseline peak VO_2 was associated with higher RV pressures, RV end-diastolic volume, (RV/left ventricular [LV] end-diastolic volume ratio), and V_E/VCO_2 ratio; it was also associated with a lower RV ejection fraction (Table III). The baseline peak VO_2 of the stenotic subgroup (69.7% ± 19.2% predicted) was slightly higher than that of the regurgitant (59.6% ± 19.2% predicted) or mixed (60.6% ± 14.6% predicted) subgroup ($P < .025$).

Changes in exercise function after TPV

Changes in exercise function parameters 6 months after TPV are summarized in Table II. Peak VO_2 and peak O_2 pulse did not change significantly after TPV. There were small but significant improvements in peak work rate and the V_E/VCO_2 ratio. Compared with the pre-TPV test, patients more often terminated exercise because of leg fatigue than difficulty breathing at 6 months (74% vs 56%, $P = .01$) after TPV. The HR and RER at peak exercise did not differ, suggesting that a similar effort was expended on the pre- and post-TPV studies.

Table III. Relationship between baseline peak VO_2 and other baseline hemodynamic echocardiographic and MRI variables

Variable	n	R	P
Age (y)	98	−0.087	.39
Mean RA pressure (mm Hg)	98	−0.41	<.0001
RV systolic pressure (mm Hg)	67	−0.43	.0002
RV end-diastolic pressure (mm Hg)	98	−0.33	.0008
Distal PA systolic pressure (mm Hg)	94	−0.27	.007
RV/LV pressure ratio	88	−0.10	.30
RV-PA gradient (mm Hg)	98	−0.027	.78
RVOT gradient (mm Hg)	95	0.26	.009
RVEDVI (mL/m^2)	77	−0.42	<.0001
LVEDVI (mL/m^2)	77	−0.050	.66
RV/LVEDVI	78	−0.36	.0009
PR fraction (%)	76	−0.093	.42
LVEF (%)	78	0.21	.056
RVEF (%)	78	0.34	.002
V_E/VCO_2 ratio at AT	94	−0.37	.002

R, Pearson correlation coefficient.

Relationship between clinical characteristics and the post-TPV improvement in peak VO_2

There were weak but significant correlations between the primary outcome (change in % predicted peak VO_2

Table IV. Correlation between changes in % predicted peak VO2, % predicted O_2 pulse, and VE/VCO_2 ratio (baseline 6 months post TPV) and baseline hemodynamic, echocardiographic, MRI and CPET variables

	Change peak VO_2			Change V_E/VCO_2 ratio		
Variables at baseline	**n**	***R***	***P***	**n**	***R***	***P***
Catheterization variables						
Mean RA pressure	98	0.34	.007	105	−0.27	.006
RV systolic pressure	98	0.06	.59	105	−0.12	.24
RV end-diastolic pressure	98	0.23	.02	105	−0.17	.09
Distal PA systolic pressure	94	0.18	.08	103	−0.03	.78
RV/LV pressure ratio	88	−0.02	.87	94	−0.05	.63
RV-PA gradient	98	−0.07	.50	105	−0.01	.94
2D echocardiogram variables						
TR severity	96	0.29	.005	102	−0.002	.99
Cardiac MRI variables						
RVEDVI	77	0.19	.10	81	−0.29	.01
LVEDVI	77	−0.09	.42	81	−0.12	.27
RV/LVEDVI	77	0.24	.03	81	−0.24	.03
PR fraction	76	0.06	.59	78	−0.02	.89
LVEF	78	−0.14	.21	82	0.19	.09
RVEF	78	−0.22	.05	82	0.21	.06
Baseline exercise variables						
% Predicted peak VO_2	98	−0.44	<.0001	105	0.15	.10
V_E/VCO_2 ratio	94	0.28	.006	105	−0.52	<.0001
% Predicted O_2 pulse	98	0.18	.08	101	0.08	.41
% Predicted peak HR	98	0.09	.37	105	0.037	.70
RER	98	0.05	.64	105	−0.0002	.99
Procedure-related changes						
Δ TR jet gradient	74	0.18	.11	79	−0.15	.18
Δ RVOT gradient	98	0.06	.76	91	−0.012	.90
Δ RVEDVI	62	−0.23	.077	66	0.12	.32
Δ LVEDVI	62	0.20	.11	66	0.03	.82
Δ LVEDVI/RVEDVI	63	−0.31	.01	67	0.15	.22
Δ PR fraction	63	−0.015	.90	65	−0.021	.86
Δ RVEF	63	0.15	.25	67	−0.16	.20
Δ LVEF	63	0.13	.31	67	−0.23	.06

Δ Indicates change from baseline to 6 months postimplantation. *2D,* 2-dimensional.

between the baseline and 6-month post-TPV exercise studies) and the baseline mean right atrial (RA) pressure, RV end-diastolic pressure, presence of severe TR at baseline, RV/LV end-diastolic volume ratio, V_E/VCO_2 ratio, baseline right ventricular ejection fraction (RVEF), and baseline peak VO_2 (Table IV and Figure 1). Post-TPV improvements in peak VO_2 were not associated with other preimplantation catheterization, echocardiographic, or MRI variables.

Although RVEF did not change after TPV, TPV implantation was associated with significant reductions in the maximum instantaneous Doppler RVOT gradient, PR fraction, and RV indexed end-diastolic volume (EDVI) (Table II). However, changes in these variables did not correlate with concomitant changes in peak VO_2 (Table IV). Similarly, changes in peak VO_2 were not related to the nature of the dominant hemodynamic lesion.

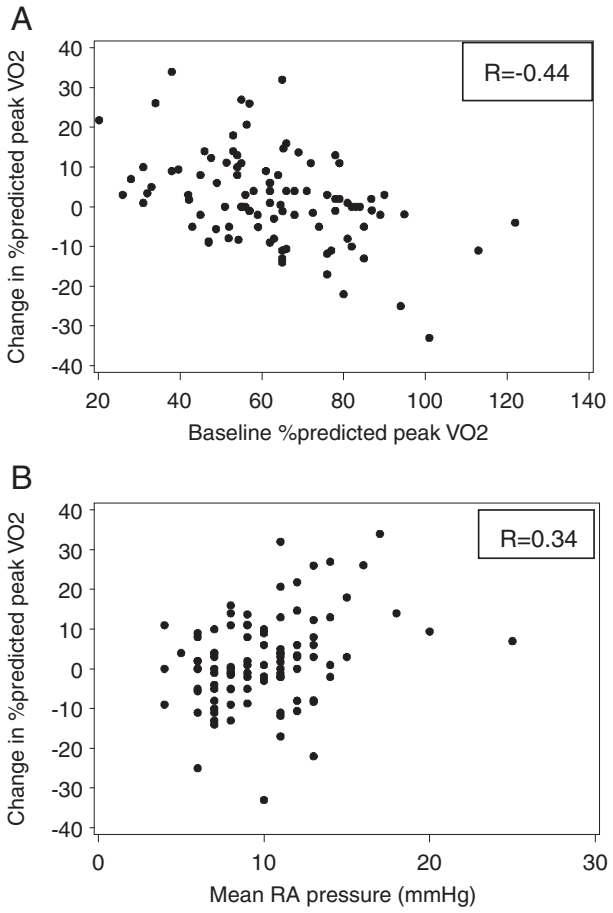
On multivariable analysis, the baseline peak VO_2 emerged as the only variable significantly associated with post-TPV change in peak VO_2. When only the catheterization and imaging variables were included in the model, the mean RA pressure emerged as the only variable associated with the change in % predicted peak VO_2 after TPV.

The relationship between TPV-associated changes in the V_E/VCO_2 ratio and the baseline/procedural variables described above resembled that observed for % predicted peak VO_2 (Table IV).

Patients with a clinically significant (>5 percentage point) improvement in peak VO_2 had significantly higher preimplant mean RA pressure, RV end-diastolic pressure, TR, RV/LV end-diastolic volume ratio, indexed RV end-diastolic volume, and distal pulmonary artery (PA) systolic pressure than did patients with smaller improvements in peak VO_2. They also had lower baseline peak VO_2 and RV ejection fraction (Table V).

Although statistically significant, the correlations between baseline clinical parameters and the TPV-related change in % predicted peak VO_2 were generally modest (Figure 1). The area under the receiver operator characteristic curve for baseline mean RA pressure was only 0.69; the sensitivity (0.76) and specificity (0.52) of the best cutoff value (9 mm Hg) were not strong.

Figure 1



A, Scatter plot of the relationship between the change in % predicted peak VO_2 and the baseline mean right atrial pressure. **B**, Scatter plot of the relationship between change in % predicted peak VO_2 and baseline % predicted VO_2.

Pulmonary performance

Pulmonary function test results are summarized in Table II. Before implant, spirometric measurements revealed a mild restrictive/obstructive pattern. Forced vital capacity (FVC), the fraction of the FVC expired in the first second (FEV_1), and the peak expiratory flow rate were reduced compared with predicted normal values. These variables did not change significantly after TPV.

Discussion

Previous studies have identified associations between RVOT dysfunction (obstruction and/or PR), RV function, and poor exercise tolerance in patients with repaired TOF.[16-19] In that patient population, the impact of surgical pulmonary valve replacement on exercise function has been small.[7,20,21] It is possible that these disappointing outcomes are due, in part, to the trauma and debilitation inevitably associated with major open heart surgery. Transcatheter pulmonary valve implantation causes less trauma and debilitation than open heart surgery and might therefore be expected to have a more immediate and positive effect upon exercise function. However, few studies have examined the impact of TPV implantation on the exercise function of patients with dysfunctional RVOT conduits.[22,23]

Consistent with previous studies in patients with palliated congenital heart disease, we found that the exercise function of patients with severe pulmonary conduit dysfunction was significantly impaired.[24,25] Indeed, peak VO_2 in our cohort was considerably lower than that reported in past series of children and young adults with repaired TOF.[26-28] Lower peak VO_2 was associated with higher right-sided pressures, RV dilation, lower RVEF, and an elevated V_E/VCO_2 ratio on preimplant evaluation. Similar relationships have been noted by previous investigators.[29-31]

Overall, there was no significant improvement in peak VO_2 after TPV. However, subjects with higher mean RA pressure, higher RV end-diastolic pressure, severe TR, lower RV ejection fraction, and higher RV/LV diastolic volume ratio tended to have improvement in peak VO_2 after TPV. A similar pattern was noted for the V_E/VCO_2 ratio at the anaerobic threshold, an index of the efficiency of gas exchange similar to the V_E/VCO_2 ratio slope, which has been found to be related to prognosis in patients with repaired TOF.[32]

We also observed that the post-TPV improvement in peak VO_2 was greatest among patients with the lowest baseline peak VO_2, with minimal additional contribution of right side of the heart parameters on multivariable analysis. We believe this finding is due, in part, to the fact that, in this patient population, a low peak VO_2 is a consequence of multiple interrelated factors (eg, RV dysfunction, excessive RV pressure, and volume overload) that combine synergistically to impair exercise function. Consequently, the impact of TPV is greatest in these patients. This theory is supported by the observed association between these right side of the heart parameters and worse baseline exercise function (Table III). In contrast, patients with higher baseline peak VO_2 tend to have milder hemodynamic abnormalities and therefore usually do not improve after TPV.

It is unlikely that the improvements in peak VO_2 observed among patients with lower baseline peak VO_2 were related solely to better patient effort because patients with suboptimal efforts were excluded from our analyses. Furthermore, changes in peak VO_2 after TPV did not correlate with concomitant changes in the peak RER, and the peak RER on the baseline and post-TPV exercise tests was virtually identical in patients with and without a $\geq$5 percentage point increase in % predicted peak VO_2. Finally, a previous study has reported

Table V. Comparison of patients with and without a clinically significant (≥5 percentage point) increase in % predicted peak VO_2

	<5% increase Mean ± SD (n = 56)	≥5% increase Mean ± SD (n = 42)	*P*
Age (y)	20.6 ± 7.7	23.7 ± 10.6	.11
Catheterization variables			
Mean RA pressure (mm Hg)	8.8 ± 2.5	11.3 ± 4.1	.0001
RV systolic pressure (mm Hg)	63.5 ± 17.3	68.2 ± 18.0	.20
RV end diastolic pressure (mm Hg)	10.9 ± 3.0	13.3 ± 4.7	.005
Distal PA systolic pressure (mm Hg)	25.3 ± 7.7	31.4 ± 13.3	.01
RV/LV pressure ratio	0.71 ± 0.17	0.73 ± 0.18	.56
RV-PA gradient (mm Hg)	37.7+16.1	35.4 ± 15.4	.47
Preimplant cardiac MRI variables			
RVEDVI (mL/m^2)	116.6 ± 29.4	152.1 ± 69.1	.01
LVEDVI (mL/m^2)	83.4 ± 28.7	77.2 ± 17.5	.24
RVEDVI/LVEDVI ratio	1.5 ± 0.4	2.0 ± 1.0	.007
RVEF (%)	46.8 ± 12.5	37.1 ± 13.4	.003
LVEF (%)	57.5 ± 10.7	54.4 ± 11.0	.23
Baseline PR fraction (%)	21.9 ± 16.6 (47)	25.2 ± 13.7	.34
Preimplant echocardiographic variables			
RVOT gradient (mm Hg)	59.7 ± 20.5	51.9 ± 19.3	.062
TR severity grade	1.1 ± 0.9	1.5 ± 0.9	.03
TR Doppler gradient (mm Hg)	65.1 ± 16.1	65.3 ± 16.2	.96
Preimplant CPET variables			
% Predicted peak VO_2	69.1 ± 19.0	54.1 ± 14.3	<.0001
V_E/VCO_2 ratio	29.6 ± 2.9	31.7 ± 5.5	.033
% Predicted O_2 pulse	90.4 ± 22.2	77.6 ± 19.2	.0046
RER	1.15 ± 0.09	1.15 ± 0.12	.89
TPV-induced changes			
Δ Doppler TR gradient (mm Hg)	−22.1 ± 15.6	−16.7 ± 14.2	.13
Δ Doppler RVOT gradient (mm Hg)	−22.1 ± 20.4	−21.4 ± 18.2	.85
Δ RVEDVI (mL/m^2)	−23.2 ± 20.5	−25.0 ± 21.9	.75
Δ LVEDVI (mL/m^2)	−2.2 ± 16.4	6.0 ± 10.7	.02
Δ RVEDVI/LVEDVI	−0.3 ± 0.4	−0.4 ± 0.3	.18
Δ RVEF (%)	−4.7 ± 12.8	1.3 ± 11.1	.054
Δ LVEF (%)	0.77 ± 8.8	3.8 ± 10.6	.24
Δ PR fraction (%)	−21.9 ± 16.2	−20.6 ± 12.8	.72
Δ RER	0.038 ± 0.068	0.017 ± 0.12	.32

that, on exercise tests separated by 1 year, the peak VO_2 of stable patients with complex congenital heart disease did not change significantly.[33] These considerations imply that the changes observed in this study were not the result of variations in patient effort or "regression to the mean."

When patients with a clinically significant improvement in peak VO_2 were compared with other patients, we once again noted that indices associated with RV dysfunction (ie, RV dilation, elevated RV filling pressures, lower RVEF, and more severe TR) were more pronounced among patients who had a clinically significant improvement in peak VO_2. In contrast, improvements in peak VO_2 were not related to TPV-induced changes in the RVOT gradient or PR fraction. These observations suggest that the improvement in peak VO_2 after TPV is related more to the presence or absence of RV decompensation in the face of the abnormally elevated workload[AU1] than to the magnitude of the pressure-volume work imposed on the RV by the dysfunctional conduit.

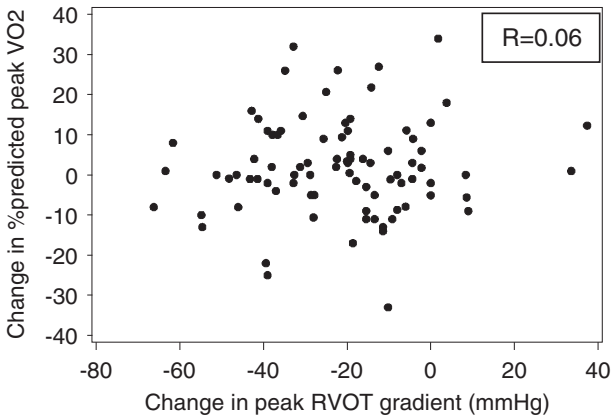
In our opinion, however, these observations do not imply that TPV implantation should be delayed until RV dysfunction is present, as it is likely that timely treatment of RV volume and/or pressure overload can prevent or forestall the development of RV dysfunction and that RV dysfunction, once present, may be irreversible.[34] Furthermore, it must be noted that the correlations between baseline RV functional parameters and post-TPV improvements in peak VO_2 were weak.

Patients with clinically significant improvements in peak VO_2 also tended to have higher distal PA pressures than patients with more modest improvements in peak VO_2. This observation may reflect that patients with distal PA stenoses and/or elevated pulmonary arteriolar resistance are particularly intolerant of the loss of pulmonary valve function and, therefore, are more likely to improve when pulmonary valve function is restored.[10,35]

A statistically significant decline in the V_E/VCO_2 ratio at the anaerobic threshold was observed after TPV implantation. In patients with repaired TOF, the V_E/VCO_2 ratio slope correlates negatively with exercise capacity, and the magnitude of the V_E/VCO_2 ratio slope elevation has been related to the severity of pulmonary blood flow maldistribution.[30,35] In our study, a decrease in the V_E/VCO_2 ratio after TPV implantation indicates that patients were able to breathe more efficiently (ie, they required less V_E to eliminate a given amount of CO_2). We speculate that restoration of pulmonary valve function and elimination of PR by the Melody valve improved pulmonary blood flow maldistribution and thereby reduced ventilation/perfusion mismatch and physiologic dead space, facilitating more efficient gas exchange between the alveoli and pulmonary capillaries.

Improved ventilatory efficiency after TPV implantation allowed patients to devote a greater portion of energy expenditure to the work of pedaling the cycle ergometer rather than to the work of breathing. Similarly, the reduction in PR/stenosis after TPV implantation allowed patients to devote less energy to the work of pumping blood during exercise. Consequently, a significant improvement in peak work rate was observed, although the increase in peak VO_2 did not achieve statistical significance. These physiologic changes may also account for the shift in the reason for exercise termination from "difficulty breathing" to "general fatigue" after TPV

Figure 2



Scatter plot of the relationship between the change in % predicted peak VO_2 and change in RVOT gradient.

implantation. It must be noted, however, that the improvements in peak work rate and the V_E/VCO_2 ratio were relatively small and of uncertain clinical significance.

Comparison with past studies

Past studies comparing pre- and postoperative exercise function in patients undergoing surgical pulmonary valve replacement produced inconsistent results. Several large studies found no improvement in peak VO_2 after surgical valve replacement.[7,20,21] Similarly, after TPV, it has been found that patients with predominant PR generally do not attain a significant increase in peak VO_2, although improvements in peak work rate and V_E/VCO_2 ratio have been reported.[22] Our findings are consistent with this experience. In contrast, among patients with predominant RVOT obstruction, small but significant improvements in peak VO_2 were detected acutely (within 1 month) and 1 year after TPV by Lurz et al[22,23]; the degree of improvement correlated with the baseline RVOT gradient. We did not observe these phenomena in our study population (Figure 2). This discrepancy may relate to the fact that patients in our stenotic subgroup had higher baseline peak VO_2 than those reported by Lurz et al. Their studies also excluded patients with mixed disease and patients who developed recurrent RVOT dysfunction,[22,23] selection biases that were not present in our series. It should also be noted that, after TPV, the peak VO_2 among patients with RVOT stenosis in that series was no better than the peak VO_2 of patients with PR. Furthermore, even after TPV and restoration of normal or near normal pulmonary valve function, the exercise capacity of the patients in their series (and ours) remained substantially lower than what was reported in previous series of postoperative patients with TOF.[26-28]

Among patients with other congenital heart defects, a similar discrepancy between the dramatic hemodynamic effects of surgical/catheterization procedures and more modest improvements in exercise capacity have often been encountered.[36-43] This discrepancy may be related to the fact that aerobic capacity is determined by skeletal muscle function as well as cardiopulmonary function and that procedures that address only 1 component of this complex physiology without addressing the other will be of limited effectiveness. Hence, cardiovascular interventions may improve a patient's potential aerobic capacity but, unless combined with a training program that addresses a patient's skeletal muscle system, will have but limited effect upon his/her actual capacity.

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References

1. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Alliance for Adult Research in Congenital Cardiology (AARCC). Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 2010;122:868-75.
2. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-81.
3. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000;356:1403-5.
4. Khambadkone S, Coats L, Taylor A, et al. Transcatheter pulmonary valve implantation in humans: initial results in 59 consecutive patients. Circulation 2005;112:1189-97.
5. Lurz P, Coats L, Khambadkone S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation 2008;117:1964-72.
6. McElhinney DB, Hellenbrand WE, Zahn EM, et al. Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation 2010;122:507-16.
7. Frigiola A, Tsang V, Bull C, et al. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? Circulation 2008;118(Suppl):182-90.
8. Coats L, Khambadkone S, Derrick G, et al. Physiological consequences of percutaneous pulmonary valve implantation: the different behaviour of volume- and pressure-overloaded ventricles. Eur Heart J 2007;28:1886-93.
9. Lurz P, Puranik R, Nordmeyer J, et al. Improvement in left ventricular filling properties after relief of right ventricle to pulmonary artery conduit obstruction: contribution of septal motion and interventricular mechanical delay. Eur Heart J 2009;30:2266-74.
10. Lurz P, Nordmeyer J, Coats L, et al. Immediate clinical and haemodynamic benefits of restoration of pulmonary valvar competence in patients with pulmonary hypertension. Heart 2009;95:646-50.

11. Zahn EM, Hellenbrand WE, Lock JE, et al. Implantation of the melody transcatheter pulmonary valve in patients with a dysfunctional right ventricular outflow tract conduit early results from the U.S. Clinical trial. J Am Coll Cardiol 2009;54:1722-9.
12. Paridon SM, Mitchell PD, Colan SD, et al. Pediatric Heart Network Investigators. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol 2008;52:99-107.
13. Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis 1984;129:S47-8.
14. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. Am Rev Resp Dis 1984;129(Suppl):S49-55.
15. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W.B. Saunders; 1997. p. 135.
16. Buys R, Cornelissen V, De Bruaene AV, et al. Measures of exercise capacity in adults with congenital heart disease. Int J Cardiol 2011; 153:26-30.
17. Eyskens B, Brown SC, Claus P, et al. The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot. Eur J Echocardiogr 2010;11: 341-5.
18. Eyskens B, Reybrouck T, Bogaert J, et al. Homograft insertion for pulmonary regurgitation after repair of tetralogy of Fallot improves cardiorespiratory exercise performance. Am J Cardiol 2000;85: 221-5.
19. Marx GR, Hicks RW, Allen HD, et al. Noninvasive assessment of hemodynamic responses to exercise in pulmonary regurgitation after operations to correct pulmonary outflow obstruction. Am J Cardiol 1988;61:595-601.
20. Geva T, Gauvreau K, Powell AJ, et al. Randomized trial of pulmonary valve replacement with and without right ventricular remodeling surgery. Circulation 2010;122(Suppl 1):S201-8.
21. Ghez O, Tsang VT, Frigiola A, et al. Right ventricular outflow tract reconstruction for pulmonary regurgitation after repair of tetralogy of Fallot: preliminary results. Eur J Cardiothorac Surg 2007;31: 654-8.
22. Lurz P, Nordmeyer J, Giardini A, et al. Early versus late functional outcome after successful percutaneous pulmonary valve implantation are the acute effects of altered right ventricular loading all we can expect? J Am Coll Cardiol 2011;57:724-31.
23. Lurz P, Giardini A, Taylor AM, et al. Effect of altering pathologic right ventricular loading conditions by percutaneous pulmonary valve implantation on exercise capacity. Am J Cardiol 2010;105:721-6.
24. Fredriksen PM, Therrien J, Veldtman G, et al. Aerobic capacity in adults with tetralogy of Fallot. Cardiol Young 2002;12:554-9.
25. Zapletal A, Samanek M, Hruda J, et al. Lung function in children and adolescents with tetralogy of Fallot after intracardiac repair. Pediatr Pulmonol 1993;16:23-30.
26. Kipps AK, Graham DA, Harrild DM, et al. Longitudinal exercise function in patients with repaired tetralogy of Fallot. Am J Cardiol 2011;108:99-105.
27. Rowe SA, Zahka KG, Manolio TA, et al. Lung function and pulmonary regurgitation limit exercise capacity in postoperative tetralogy of Fallot. J Am Coll Cardiol 1991;17:461-6.
28. Wessel HU, Paul MH. Exercise studies in tetralogy of Fallot: a review. Pediatr Cardiol 1999;20:39-47.
29. Meadows J, Powell AJ, Geva T, et al. Cardiac magnetic resonance imaging correlates of exercise capacity in patients with operatively repaired tetralogy of Fallot. Am J Cardiol 2007;100: 1446-50.
30. Rhodes J, Dave A, Pulling MC, et al. Effect of pulmonary artery stenoses on the cardiopulmonary response to exercise following repair of tetralogy of Fallot. Am J Cardiol 1998;81:1217-9.
31. Clark AL, Gatzoulis MA, Redington AN. Ventilatory responses to exercise in adults after repair of tetralogy of Fallot. Br Heart J 1995; 73:445-9.
32. Giardini A, Specchia S, Tacy TA, et al. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. Am J Cardiol 2007;99:1462-7.
33. Rhodes J, Curran TJ, Camil L, et al. Sustained effects of cardiac rehabilitation in children with serious congenital heart disease. Pediatrics 2006;118:e586-93.
34. Therrien J, Siu SC, McLaughlin PR, et al. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? J Am Coll Cardiol 2000;36:1670-5.
35. Sutton NJ, Peng L, Lock JE, et al. Effect of pulmonary artery angioplasty on exercise function after repair of tetralogy of Fallot. Am Heart J 2008;155:182-6.
36. Barber G, Danielson GK, Puga FJ, et al. Pulmonary atresia with ventricular septal defect: preoperative and postoperative responses to exercise. J Am Coll Cardiol 1986;7:630-8.
37. Helber U, Baumann R, Seboldt H, et al. Atrial septal defect in adults: cardiopulmonary exercise capacity before and 4 months and 10 years after defect closure. J Am Coll Cardiol 1997;29: 1345-50.
38. Jonsson B, Lee SJ. Haemodynamic effects of exercise in isolated pulmonary stenosis before and after surgery. Br Heart J 1968;30: 60-6.
39. Matthys D. Pre- and postoperative exercise testing of the child with atrial septal defect. Pediatric Cardiology 1999;20:22-5.
40. Rhodes J, Patel H, Hijazi ZM. Effect of transcatheter closure of atrial septal defect on the cardiopulmonary response to exercise. Am J Cardiol 2002;90:803-6.
41. Zellers TM, Driscoll DJ, Mottram CD, et al. Exercise tolerance and cardiorespiratory response to exercise before and after the Fontan operation. Mayo Clin Proc 1989;64:1489-97.
42. Goldberg SJ, Mendes F, Hurwitz R. Maximal exercise capability of children as a function of specific cardiac defects. Am J Cardiol 1969; 23:349-53.
43. Longmuir PE, Turner JA, Rowe RD, et al. Postoperative exercise rehabilitation benefits children with congenital heart disease. Clin Invest Med 1985;8:232-8.