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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.
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. 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.

Metabolic measurements

Expired gases were measured for 3 minutes of quiet rest and throughout the exercise protocol. Oxygen consumption (VO2), carbon dioxide production (VCO2), and minute ventilation (V
) were measured on a breath-by-breath basis. Peak VO2 was defined as the highest VO2 achieved by the subject during the test. Ventilatory anaerobic threshold was measured with V-slope method when it could be accurately determined. Values for VO2 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 similar protocol. The ratio of Ve to VCO2 (Ve/VCO2 ratio) was measured at the ventilatory anaerobic threshold. The respiratory exchange ratio (RER; VCO2/VO2 ratio) was measured continuously. The O2 pulse (VO2/heart rate [HR]) was measured at peak VO2. The O2 pulse is equal to the product of forward stroke volume and the arterial-venous O2 content difference. Because the arterial-venous O2 content difference at peak exercise varies little among untrained subjects, the O2 pulse may be used as a surrogate for forward stroke volume at peak exercise. Arterial O2 saturation was measured continuously with a pulse oximeter placed on the finger or ear.

To exclude data from patients who stopped exercising for noncardiovascular reasons (ie, before approaching their cardio-

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.

vascular 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).

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 VO2 (% 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 VO2 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 VO2, which was defined as a ≥5 percentage point increase in peak VO2 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),
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 $\geq 1.05$ or HR $\geq 85\%$ 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 $V_{E}/V_{CO2}$ 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 $V_{E}/V_{CO2}$ 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>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>$R$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>98</td>
<td>-0.087</td>
<td>.39</td>
</tr>
<tr>
<td>Mean RA pressure (mm Hg)</td>
<td>98</td>
<td>-0.41</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>67</td>
<td>-0.43</td>
<td>.0002</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mm Hg)</td>
<td>98</td>
<td>-0.33</td>
<td>.0008</td>
</tr>
<tr>
<td>Distal PA systolic pressure (mm Hg)</td>
<td>94</td>
<td>-0.27</td>
<td>.007</td>
</tr>
<tr>
<td>RV/LV pressure ratio</td>
<td>88</td>
<td>-0.10</td>
<td>.30</td>
</tr>
<tr>
<td>RV-Pa gradient (mm Hg)</td>
<td>98</td>
<td>-0.027</td>
<td>.78</td>
</tr>
<tr>
<td>RVOT gradient (mm Hg)</td>
<td>95</td>
<td>0.26</td>
<td>.009</td>
</tr>
<tr>
<td>RVEDVI (mL/m$^2$)</td>
<td>77</td>
<td>-0.42</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LVEDVI (mL/m$^2$)</td>
<td>77</td>
<td>-0.050</td>
<td>.66</td>
</tr>
<tr>
<td>LV/TVEDVI</td>
<td>78</td>
<td>-0.36</td>
<td>.0009</td>
</tr>
<tr>
<td>PR fraction (%)</td>
<td>76</td>
<td>-0.093</td>
<td>.42</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>78</td>
<td>0.21</td>
<td>.056</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>78</td>
<td>0.34</td>
<td>.002</td>
</tr>
<tr>
<td>$V_{E}/V_{CO2}$ ratio at AT</td>
<td>94</td>
<td>-0.37</td>
<td>.002</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD (median).

AT, Anaerobic threshold; EF, ejection fraction.
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, V̇E/V̇CO₂ ratio, baseline right ventricular ejection fraction (RVEF), and baseline peak VO₂ (Table IV and Figure 1). Post-TPV improvements in peak VO₂ 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 VO₂ (Table IV). Similarly, changes in peak VO₂ were not related to the nature of the dominant hemodynamic lesion.

On multivariable analysis, the baseline peak VO₂ emerged as the only variable significantly associated with post-TPV change in peak VO₂. 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 VO₂ after TPV.

The relationship between TPV-associated changes in the V̇E/V̇CO₂ ratio and the baseline/procedural variables described above resembled that observed for % predicted peak VO₂ (Table IV).

Patients with a clinically significant (>5 percentage point) improvement in peak VO₂ 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 VO₂. They also had lower baseline peak VO₂ and RV ejection fraction (Table V).

Although statistically significant, the correlations between baseline clinical parameters and the TPV-related change in % predicted peak VO₂ 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.
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 (FEV1), 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. In that patient population, the impact of surgical pulmonary valve replacement on exercise function has been small. 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.

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. Lower peak VO2 was associated with higher right-sided pressures, RV dilation, lower RVEF, and an elevated Vp/VCO2 ratio on preimplant evaluation. Similar relationships have been noted by previous investigators.

Overall, there was no significant improvement in peak VO2 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 VO2 after TPV. A similar pattern was noted for the Vp/VCO2 ratio at the anaerobic threshold, an index of the efficiency of gas exchange similar to the Vp/VCO2 ratio slope, which has been found to be related to prognosis in patients with repaired TOF.

We also observed that the post-TPV improvement in peak VO2 was greatest among patients with the lowest baseline peak VO2, 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 VO2 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 VO2 tend to have milder hemodynamic abnormalities and therefore usually do not improve after TPV.

It is unlikely that the improvements in peak VO2 observed among patients with lower baseline peak VO2 were related solely to better patient effort because patients with suboptimal efforts were excluded from our analyses. Furthermore, changes in peak VO2 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 ≥5 percentage point increase in % predicted peak VO2. Finally, a previous study has reported
that, on exercise tests separated by 1 year, the peak VO2 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 VO2 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 VO2. In contrast, improvements in peak VO2 were not related to TPV-induced changes in the RVOT gradient or PR fraction. These observations suggest that the improvement in peak VO2 after TPV is related more to the presence or absence of RV decompensation in the face of the abnormally elevated workload 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 VO2 were weak.

Patients with clinically significant improvements in peak VO2 also tended to have higher distal PA pressures than patients with more modest improvements in peak VO2. 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 V̇E/V̇CO2 ratio at the anaerobic threshold was observed after TPV implantation. In patients with repaired TOF, the V̇E/V̇CO2 ratio slope correlates negatively with exercise capacity, and the magnitude of the V̇E/V̇CO2 ratio slope elevation has been related to the severity of pulmonary blood flow maldistribution.30,35 In our study, a decrease in the V̇E/V̇CO2 ratio after TPV implantation indicates that patients were able to breathe more efficiently (ie, they required less V̇E to eliminate a given amount of CO2). 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 VO2 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.
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**