Biventricular Response After Pulmonary Valve Replacement for Right Ventricular Outflow Tract Dysfunction

Is Age a Predictor of Outcome?

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Background—The timing of pulmonary valve replacement (PVR) for free pulmonary incompetence in patients with congenital heart disease remains a dilemma for clinicians. We wanted to assess the determinants of improvement after PVR for pulmonary regurgitation over a wide range of patient ages and to use any identified predictors to compare clinical outcomes between patient groups.

Methods and Results—Seventy-one patients (mean age 22 ± 11 years; range, 8.5 to 64.9; 72% tetralogy of Fallot) underwent PVR for severe pulmonary regurgitation. New York Heart Association class improved after PVR (median of 2 to 1, P < 0.0001). MRI and cardiopulmonary exercise testing were performed before and 1 year after intervention. After PVR, there was a significant reduction in right ventricular volumes (end diastolic volume 142 ± 43 to 91 ± 18, end systolic volume 73 ± 33 to 43 ± 14 mL/m², P < 0.0001), whereas left ventricular end diastolic volume increased (66 ± 12 to 73 ± 13 mL/m², P < 0.0001). Effective cardiac output significantly increased (right ventricular: 3.0 ± 0.8 to 3.3 ± 0.8 L/min, P = 0.013 and left ventricular: 3.0 ± 0.6 to 3.4 ± 0.7 L/min, P < 0.0001). On cardiopulmonary exercise testing, ventilatory response to carbon dioxide production at anaerobic threshold improved from 35.9 ± 5.8 to 34.1 ± 6.2 (P = 0.008). Normalization of ventilatory response to carbon dioxide production was most likely to occur when PVR was performed at an age younger than 17.5 years (P = 0.013).

Conclusions—A relatively aggressive PVR policy (end diastolic volume <150 mL/m²) leads to normalization of right ventricular volumes, improvement in biventricular function, and submaximal exercise capacity. Normalization of ventilatory response to carbon dioxide production is most likely to occur when surgery is performed at an age ≤17.5 years. This is also associated with a better left ventricular filling and systolic function after surgery. (Circulation. 2008;118[suppl 1]:S182–S190.)

Key Words: echocardiography ■ exercise ■ MRI ■ pulmonary regurgitation ■ surgical repair

The dilemma of when to treat patients with free pulmonary incompetence, presenting late after repair of right ventricular outflow tract obstruction (in particular treated tetralogy of Fallot), is one that faces all congenital heart disease clinicians. Although we have learned that in the long-term, pulmonary incompetence is detrimental, leading to an increased incidence of adverse events1–3 (death, sustained arrhythmias, increasing symptoms), the conventional thinking has been that the benefit of treating free pulmonary incompetence is outweighed by the potential risk of surgical pulmonary valve replacement and the lack of longevity of this treatment (conduit dysfunction within 10 to 15 years that exposes patients to multiple operations over their life).4–6 We have thus often delayed pulmonary valve replacement (PVR) until patients develop symptoms. However, there is the potential that symptomatic improvement after surgery may be limited due to the fact that the right ventricle has been chronically exposed to pulmonary incompetence.

More recently, there has been a shift in this risk/benefit continuum. Operative mortality and morbidity are now small with modern operative methods and postoperative care,5,7 and conduit life can now be extended using new noninvasive percutaneous approaches to treat conduit dysfunction.8 Thus, the timing of treatment can be based more on the patients’ normalization of parameters in terms of subjective and quantitative measures of outcome and physiological response to PVR.
In this study, we have set out to assess the effect of surgical PVR over a wide range of patient ages investigating both children and adults with systematic clinical, imaging (echocardiography, MRI), and quantitative exercise testing. The aim of the study was to attempt to identify any predictors that would suggest an increased likelihood of patient improvement after operation and to use any identified predictors to compare clinical outcomes between patient groups.

Methods

Patient Population
Between January 2004 and September 2007, 71 consecutive patients (mean age 22±11 years; range, 8.5 to 64.9 years; 39 males) were prospectively studied before and 1 year after surgical PVR (Table 1). In our clinical practice, all patients with free pulmonary regurgitation (PR) and evidence of right ventricular (RV) dilatation at echocardiography undergo a “right ventricular outflow tract” (RVOT) assessment with MRI, tissue Doppler imaging, and cardiopulmonary exercise test. Those patients who were symptomatic and showed reduced exercise capacity were selected for surgery. In the absence of symptoms, surgery was indicated in the presence of significant RV dilatation (RV/left ventricular end diastolic ratio >2) and reduced parameters at cardiopulmonary exercise test. Patient characteristics are summarized in Table 1.

Additional procedures at the time of definitive repair included patch enlargement of the pulmonary trunk (n=1), of the right pulmonary artery (PA; n=1), or left PA (n=2) and atrial septal defect (ASD) closure (n=2). Subsequent to complete repair, 5 patients underwent further operative treatments (RV-PA conduit, n=3; closure of residual ventricular septal defect (VSD), n=1; and tricuspid valve [TV] annuloplasty, n=1). Revision of branch PAs was performed by surgical reconstruction in 3 patients, balloon dilatation in one, and stenting in 3. Ablation for atrial flutter was performed in one patient and insertion of an automatic internal cardioverter–defibrillator for sustained ventricular tachycardia (VT) in one patient. One patient was counted twice in the analysis as he underwent PVR twice.

The local research ethics committees approved the study, and all subjects (and/or a parent/guardian) gave informed consent.

Statement of Responsibility
The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Echocardiography
Echocardiography was performed using a VIVID 7 machine (GE Medical Systems, Milwaukee, Wis). We assessed the following: gradient across the RVOT; severity of tricuspid valve regurgitation (visually classified as absent, trivial, mild, moderate, or severe using color Doppler); myocardial systolic (s) and diastolic (e, a) velocities using tissue Doppler imaging (frame rate 200±25 s\(^{-1}\); tricuspid and mitral valve annuli); and isovolumic acceleration (calculated as described by Vogel et al\(1\)). For tissue Doppler imaging, measurements were obtained from offline analysis as a mean of 3 consecutive cardiac cycles (Echopac; GE Vingmed, Horten, Norway).

MRI
MRI was performed using an I.5-T MR scanner (Avanto; Siemens Medical Systems, Erlangen, Germany).

Assessment of Ventricular Volumes and Function Using Cine MRI
Retrospective gated steady-state free precession cine MRIs of the heart were acquired in the vertical long-axis, 4-chamber view and the short-axis view covering the entirety of both ventricles (9 to 12 slices). Image parameters were TR=2.2 ms; TE=1.1 ms; flip angle=78\(^{\circ}\); slice thickness=6 to 8 mm; matrix=192×312; field of view=300 to 380 mm; and temporal resolution=25 phases acquired during a single breath-hold. Assessment of left ventricular (LV) and RV volumes was performed by manual segmentation of short-axis cine images at end diastole and end systole (Argus; Siemens Medical Systems). End diastolic and end systolic volumes were calculated by use of Simpson’s rule for each ventricle, and from these volumes, stroke volume (SV) and ejection fraction (EF) were calculated. Where pulmonary regurgitation was present, an effective RV SV was calculated to reflect the net forward blood flow into the pulmonary arteries as follows: effective RV SV=RV SV–PR volume. Cardiac
output (CO) was calculated by multiplying the effective arterial forward flow by the heart rate.

**MR Flow Quantification**

PA and aortic flow data were acquired by use of a flow-sensitive gradient-echo sequence (TR, 27 ms; TE, 3.2 ms; flip angle, 30°; slice thickness, 5 mm; and matrix, 256×240) during free breathing. Image planes were located at the midpoint of the main PA and just above the sinus level of the ascending aorta. Through-plane flow data (30 phases per cardiac cycle) were acquired by use of retrospective cardiac gating. Arterial blood flow was calculated from phase contrast images by use of a semiautomatic vessel-edge-detection algorithm (Argus; Siemens Medical Systems) with operator correction. PR fraction was calculated as percent backward flow over forward flow. All volume and flow measurements were indexed for body surface area and expressed in mL/beat/m².

**Objective Assessment of Exercise Capacity:**

**Metabolic Exercise Testing**

Cardiopulmonary exercise testing was performed on the same day as echocardiography on an electronically braked bicycle ergometer with respiratory gas exchange analysis before and 1 year after PVR. An Ergoline 900 (Medgraphics, St Paul, Minn) was used in the children’s hospital and a SensorMedics Vmax 229 (Yorba Linda, Calif) for the adult patients. A ramp protocol comprising an initial period of loadless cycling to permit equilibration was used. A period of active recovery (slow cycling) followed maximal exertion. Heart rate, blood pressure, and oxygen saturation were monitored in all subjects for the duration of the test. Peak oxygen uptake (VO₂ max), anaerobic threshold, and ventilatory response to carbon dioxide production (VE/VAst) were derived from respiratory gas analysis during maximal exercise testing; VO₂max, was measured as ratio at the anaerobic threshold. Anaerobic threshold (AT) was determined by use of the modified V-slope method. Peak heart rate, blood pressure, and workload (Watts) achieved were recorded.

**Surgical Technique**

The surgical technique has been described before. Most cases were performed under routine cardiopulmonary bypass on the beating heart with ascending aortic and bicaval cannulation at 32°C. In case of residual ventricular septal defect or other intracardiac lesion requiring attention, aortic crossclamping with cold blood cardioplegia was used. Midline conduit and hemorrhage during redo sternotomy warranted femorofemoral bypass.

Pulmonary homograft insertion is the preferred surgical option in our institutions. The native main pulmonary trunk was dissected out and circumferentially transected close to the ventriculoarterial junction. The branch pulmonary arteries were sized and dealt with if necessary (n=10). A longitudinal incision was made into the proximal outflow tract. Any hypertrophied muscular trabeculations in the subjunctional region were divided to create a widely open pathway. In patients with aneurysmal RVOT patch, the akinetic thin area was excised leaving a small fibrous rim at the muscular margin followed by plication with 4-0 Prolene to reconstruct the outflow tract (n=48). This infundibuloplasty aims to improve the distorted right ventricular outflow tract geometry and reduce the cavity size. The homograft was tailored in length and sutured to the distal pulmonary trunk using 5-0 Prolene. The proximal end of the homograft valve was inserted within the newly created muscular “sleeve” for functional support. The anatomic placement of the pulmonary homograft should offer good hemodynamics and hopefully longevity. Patients with severe tricuspid regurgitation underwent concomitant valve repair (n=2). Patients with significant atrial or ventricular arrhythmia received antiarrhythmic surgery using cryoablation (n=1).

**Data and Statistical Analysis**

Statistical analysis was performed using SPSS version 14.0 for Windows (SPSS, Chicago, Ill). The paired Student t test was performed to compare parameters before and after PVR. For ordinal data within patients, pre- and postprocedure, the Wilcoxon signed rank test was used to calculate a statistical significance. For categorical data between groups, we used the χ² test. A probability value <0.05 has been considered statistically significant.

To explore for the presence of a threshold beyond which normalization (within 2 SD of normal values after PVR) of exercise parameters became less likely, we used receiver operating characteristic curves for the following selected parameters: age at primary repair, age at PVR, time between complete repair and PVR, biventricular volumes (end diastolic volume, end systolic volume), and function (EF, CO). This required presenting exercise parameters as z-scores using published normal values for age- and sex-matched patients. For the exercise parameter VE/VO₂max, because normal values are not available for the population <20 years of age, we explored possible thresholds under 3 different assumptions about the pattern of variation of VE/VO₂max with age in those younger than 20 years. We first extrapolated the values from those obtained in patients aged between 20 and 80 years assuming a linear relation simply continued to hold below the age covered by the data. Under the second assumption, we assumed that values for those aged 20 years could be used for our neonated population. Finally, aware of the fall of VE/VO₂max between ages 9 and 11 documented by Rowland, we assumed that VE/VO₂max followed the same pattern. Using the receiver operating characteristic curves, we were thus able to explore 3 possible scenarios.

**Results**

**Whole Patient Population (n=71)**

No early or late mortality was seen in our patient population to date. All surgical data are shown in Table 1. Aortic crossclamping was performed in 4 patients who underwent concomitant procedures: aortic valve replacement with a 21 mm St Jude bileaflets mechanical prosthesis (n=1), ASD closure (n=1), further enlargement of pulmonary arteries (n=1), and resection of residual trabeculations (n=1). The aneurysmal RVOT patch was resected in 48 patients. In 2 patients, an automatic internal cardioverter-defibrillator lead was inserted for previously documented ventricular arrhythmias. In the early postoperative phase, one patient had torsion of the pulmonary homograft that required replacement with a Hancock conduit; in one patient, there was a significant pericardial effusion that required subsequent drainage; and one patient had a pleural effusion that was treated conservatively.

At 1 year after surgery, New York Heart Association class was significantly improved from a median of 2 to a median of 1 (P<0.0001); for the whole cohort of patients, 44 improved their functional class, 23 remained in the same class, and in 2 patients, New York Heart Association class became worse (2 patients were lost to follow-up; Figure 1).

Of the 71 patients who underwent PVR, 6 did not have a 1-year follow-up MRI scan; 2 patients had automatic internal cardioverter-defibrillators, 2 patients had postoperative care elsewhere, and 2 patients were lost to follow-up. Five patients (7%) had significant recurrent pulmonary regurgitation (regurgitation fraction ≥30%) at 1-year follow-up. We excluded these patients from our subsequent analysis because the presence of significant pulmonary incompetence may affect the postoperative assessment of these patients, and our aim was to assess the functional changes when pulmonary incompetence is treated.

Therefore, a total number of 60 patients have been studied and included in our results.
 Patients With Good Relief of Pulmonary Regurgitation and Before and After Data (n=60)

MRI Results (n=60)

Before intervention, the mean indexed RV end diastolic volume was 142±43 mL/m², and mean regurgitant fraction was 41±9% (Table 2).

One year after PVR, RV end diastolic volume was within the normal range in 50 of the 60 patients and RV end systolic volume was within the normal range in 36 of the 60 patients (Figure 2). There was a significant improvement in RV indices of systolic function (EF, effective SV, and effective CO). RV-effective CO increased from 3.0±0.8 to 3.3±0.8 (P=0.013). On the systemic side, there was a significant increase in LV end diastolic volume (from 66±12 to 73±13 mL/m², P<0.0001) with a significant improvement in LV indices of systolic function (EF, effective SV, and effective CO). LV-effective CO increased from 3.0±0.6 to 3.4±0.7 (P<0.0001).

Cardiopulmonary Exercise Test Results (n=57)

Three patients did not perform a maximal exercise test and have therefore been excluded (Table 3). Before surgery, the mean Vo max was 25±10 mL/Kg/min, mean AT was 15±5 mL/Kg/min, and mean Ve/VCO₂ was 35.9±5.8. After PVR, there were no changes in Vo max or AT at 1 year, whereas Ve/VCO₂ improved (from 35.9±5.8 to 34.1±6.2, P=0.008; Table 3).

Echocardiographic Results (n=60)

Before surgery, RV and LV myocardial systolic and diastolic velocities were significantly reduced compared with normal values in healthy subjects (Table 4). Isovolumic acceleration was also reduced (RV: 0.6±0.3 versus 1.8±0.5 and LV: 0.9±0.5 versus 1.3±0.3, respectively). After PVR, there was a significant change only in RV and LV early diastolic myocardial velocities. RV and LV isovolumic acceleration did not change. There were no changes in the gradient across the RV outflow tract or in the degree of tricuspid valve regurgitation.

Exploration of Predictors

Interrogation of cardiopulmonary exercise test data demonstrated that some patients had a submaximal exercise capacity (Ve/VCO₂) within the normal range after surgery. After performing a receiver operating characteristic analysis (Figure 3), age at PVR and time between complete repair and PVR were the only parameters able to predict which patients were more likely to have Ve/VCO₂ values in the normal range. With the 3 different possible sets of assumptions about the normal ranges pertaining to patients younger than 20 years of age, all the receiver operating characteristic analyses gave the same cutoff. Age at PVR ≥17.5 had a sensitivity of 87% and a specificity of 87% in predicting normalization of Ve/VCO₂ after surgery under the first assumption for normal values, a sensitivity of 75% and specificity of 83% under the second assumption, and finally a sensitivity of 72% and specificity of 87% under the third assumption. The interval between complete repair and PVR (14.8 years) gives the same cutoff for the subsequent patient analysis.

The whole patient cohort was then divided in 2 groups to establish whether the increased likelihood of submaximal exercise capacity normalization was associated with any differences in MR, cardiopulmonary exercise test, and echo parameters: Group 1 (n=26) consisted of those patients who were younger than 17.5 years at PVR; Group 2 (n=34) consisted of those patients who were older than

Table 2. MRI Parameters Pre- and Post-PVR (n=60)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre</th>
<th>Post</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>75±11</td>
<td>74±12</td>
<td>0.622</td>
</tr>
<tr>
<td>RV EDV, mL/m²</td>
<td>142±43</td>
<td>91±18</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV ESV, mL/m²</td>
<td>73±33</td>
<td>43±14</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV effSV, mL/m²</td>
<td>40±10</td>
<td>45±9</td>
<td>0.004</td>
</tr>
<tr>
<td>RV EF, %</td>
<td>51±10</td>
<td>54±7</td>
<td>0.016</td>
</tr>
<tr>
<td>RV CO, mL/min</td>
<td>3.0±0.8</td>
<td>3.3±0.8</td>
<td>0.013</td>
</tr>
<tr>
<td>LV EDV, mL/m²</td>
<td>66±12</td>
<td>73±13</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV ESV, mL/m²</td>
<td>26±8</td>
<td>26±8</td>
<td>0.532</td>
</tr>
<tr>
<td>LV effSV, mL/m²</td>
<td>40±7</td>
<td>46±8</td>
<td>0.0001</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>61±8</td>
<td>64±7</td>
<td>0.003</td>
</tr>
<tr>
<td>LV CO, mL/min</td>
<td>3.0±0.6</td>
<td>3.4±0.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV/LV EDV</td>
<td>2.2±0.5</td>
<td>1.2±0.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>PR, %</td>
<td>41±9</td>
<td>5±7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

EDV indicates end diastolic volume; ESV, end systolic volume; effSV, effective stroke volume.
17.5 years at PVR. Table 5 summarizes the different clinical characteristics.

**Subanalysis for Groups 1 and 2**

Presurgery, there were no significant differences in RV end diastolic volume (143 ± 42 in Group 1 versus 141 ± 44 in Group 2, not significant), RV end systolic volume, and RV EF between the 2 groups (Table 6). PR fraction was significantly higher in the younger patients (Group 1) compared with the older patients (PR = 45 ± 8 versus 39 ± 9%, respectively, P = 0.009).

LV end diastolic volume (62 ± 11 versus 69 ± 10 mL/m², P = 0.01) and end systolic volume (23 ± 8 versus 28 ± 8, P = 0.035) were smaller in younger patients.

After surgery, younger patients had a more significant increase in LV end diastolic volume (12.2 ± 9.7 versus 3.7 ± 11.0 mL/m², P = 0.003). These patients also had a greater improvement in LV effective SV (effective LV SV: 10.1 ± 7.1 versus 4.4 ± 8.2 mL/m², P = 0.006) and LV CO (0.8 ± 0.6 versus 0.2 ± 0.7 L/min, P = 0.002) compared with the older group.

On cardiopulmonary exercise test, before intervention, younger patients had a significant higher VO_max and AT compared with older patients (29.0 ± 9.0 versus 22.5 ± 10 P = 0.013 and 17.8 ± 4.2 versus 12.3 ± 4.5, P < 0.0001, respectively). VE/VCO₂ was also significantly lower in the younger group (P = 0.003) who had a further significant improvement after PVR (VE/VCO₂ decreased from 33.2 ± 3.0 to 30.6 ± 2.9, P = 0.004 in Group 1, whereas from 37.0 ± 6.2 to 35.7 ± 6.9, P = 0.166 in Group 2). These results were mirrored by the mean z-scored values (average of the 3 different assumptions): z-scored VE/VCO₂ decreased from 2.7 ± 1.1 to 1.9 ± 0.8 (P = 0.003) in Group 1 versus 4.5 ± 2.2 to 4.0 ± 2.2 (P = 0.081)

**Table 3. Cardiopulmonary Exercise Test Results (n=57)**

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂, mL/kg/min</td>
<td>25 ± 10</td>
<td>25 ± 9</td>
<td>0.350</td>
</tr>
<tr>
<td>AT, mL/kg/min</td>
<td>15 ± 5</td>
<td>14 ± 6</td>
<td>0.148</td>
</tr>
<tr>
<td>VO₂/VCO₂</td>
<td>35.9 ± 5.8</td>
<td>34.1 ± 6.1</td>
<td>0.008</td>
</tr>
<tr>
<td>VE, L/min</td>
<td>58 ± 22</td>
<td>58 ± 20</td>
<td>0.811</td>
</tr>
<tr>
<td>Workload, watts</td>
<td>120 ± 54</td>
<td>124 ± 49</td>
<td>0.161</td>
</tr>
<tr>
<td>Peak heart rate, beats/min</td>
<td>154 ± 41</td>
<td>163 ± 24</td>
<td>0.053</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>46 ± 14</td>
<td>43 ± 11</td>
<td>0.021</td>
</tr>
<tr>
<td>RER</td>
<td>1.07 ± 0.3</td>
<td>1.13 ± 0.9</td>
<td>0.044</td>
</tr>
</tbody>
</table>

VO₂ indicates oxygen consumption; VE, ventilation; RER, respiratory exchange ratio.

**Table 4. Echocardiographic Parameters Before and After PVR (n=60)**

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV s vel, cm/s</td>
<td>6.4 ± 1.7</td>
<td>6.6 ± 8.7</td>
<td>0.890</td>
</tr>
<tr>
<td>TV t vel, cm/s</td>
<td>7.6 ± 2.1</td>
<td>4.7 ± 2.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV IVA, m/s²</td>
<td>0.62 ± 0.34</td>
<td>0.58 ± 0.31</td>
<td>0.948</td>
</tr>
<tr>
<td>MV s vel, cm/s</td>
<td>6.5 ± 2.0</td>
<td>5.9 ± 1.6</td>
<td>0.097</td>
</tr>
<tr>
<td>MV e vel, cm/s</td>
<td>11.1 ± 2.8</td>
<td>9.5 ± 2.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>RVOT vel, m/s²</td>
<td>3.7 ± 1.8</td>
<td>4.1 ± 1.8</td>
<td>0.180</td>
</tr>
<tr>
<td>LV IVA, m/s²</td>
<td>0.85 ± 0.50</td>
<td>0.78 ± 0.43</td>
<td>0.423</td>
</tr>
<tr>
<td>RVOT vel, m/s²</td>
<td>2.0 ± 0.6</td>
<td>1.9 ± 0.5</td>
<td>0.444</td>
</tr>
<tr>
<td>TR vel</td>
<td>2.8 ± 0.4</td>
<td>2.6 ± 0.3</td>
<td>0.191</td>
</tr>
</tbody>
</table>

TV s vel indicates myocardial systolic velocity; e vel, myocardial early diastolic velocity; a vel, myocardial late diastolic velocity; IVA, isovolumic acceleration; TR, tricuspid regurgitant jet.
in Group 2 (Figure 4). In both groups, there were no changes in AT and Vo max after PVR.

On echocardiography, no differences were seen in pre- and post-systolic and diastolic myocardial velocities as well as in isovolumic acceleration between the 2 groups.

**Discussion**

With this study, we have shown that surgical PVR for PR can be performed safely with no mortality and little morbidity. After surgery, most patients felt better with an improvement in the functional, New York Heart Association class.

In those patients who had effective relief of PR, we have shown that RV volumes normalize in the majority of patients after surgery. Importantly, we have also shown for the first time that parameters of RV performance (EF and CO) also improve significantly. This differs from the previous literature, in which little alteration in RV EF has been reported.19-23

The main difference between our study population and that of others is that we chose to operate on patients with smaller (although significantly dilated) end diastolic volumes. Although the majority of our patients have undergone RVOT remodeling at surgery, this has also been the case in the recently published literature, and even in these studies, no improvement in RV EF has been seen.19,22

Because of the RVOT resected surgery, analysis of RV physiological changes may be difficult to interpret. We have therefore focused much of our analysis on LV parameters and quantitative exercise capacity. Again, for those patients who had successful relief of PR, we have shown improvement in LV filling and LV systolic function (EF and CO) after surgery. Interestingly, these improvements in LV function at rest are not mirrored by improvements in maximal exercise capacity, as we7 and others24 have previously demonstrated. However, we have now shown for the first time that the submaximal exercise parameter VE/VCO2 does improve, improvements that are most likely to reflect better lung and peripheral perfusion related to the increased biventricular effective cardiac output. The VE/VCO2 parameter has been shown to be the most powerful predictor of mortality and morbidity in noncyanotic patients with congenital heart disease25 and in patients with tetralogy of Fallot.26

Using this normalization in VE/VCO2 as a clinical outcome, we have demonstrated that those patients who are younger than 17.5 years old, at the time of PVR, are more likely to be left with this exercise parameter within the normal range after surgery. Whether this corresponds with improvement in long-term outlook will have to be the subject of further study. This age cutoff is most likely a surrogate that reflects a shorter exposure of the ventricles to altered loading conditions. Unfortunately, it is not possible to be certain that the observed differences favoring younger patients are related only to the chronicity of PR, because age at PVR is confounded with...
many other changes in the surgical management of patients over the last 30 years. Younger patients had primary repair at a younger age so their ventricles have been exposed to cyanosis and pressure overload for a shorter time. They have benefitted from improvements in surgical techniques, better myocardial protection, and a more extensive use of a transatrial approach with smaller right infundibulotomy and transannular patches in recent years. Moreover, we cannot conclude from our data that there is an age beyond which a patient is “too old” for any expectation of improvement because occasional older patients had a very satisfactory result.

However, using this age cutoff to divide our patient population, we show that physiologically, the younger patient group benefits more from PVR (better LV filling and CO). Interestingly, when the baseline RV parameters are compared, there are no differences in the mean presurgical volumes (end diastolic volume and end systolic volume) between the groups. There is, however, a significant difference in the baseline pulmonary regurgitant fraction, which is higher in the younger patient population. We hypothesize that this higher regurgitant fraction signifies a higher ventricular compliance (possibly a less fibrosed ventricle) than in the older patient group that ultimately leads to the better response

Table 6. MRI Parameters in Group 1 (n=26) (age at PVR ≤17.5 years) and in Group 2 (n=34; age at PVR >17.5 years)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Pre</th>
<th>Group 1 Post</th>
<th>P Value</th>
<th>Group 2 Pre</th>
<th>Group 2 Post</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>76±14</td>
<td>77±11</td>
<td>0.902</td>
<td>73±10</td>
<td>72±11</td>
<td>0.425</td>
</tr>
<tr>
<td>RV EDV, mL/m²</td>
<td>143±42</td>
<td>91±16</td>
<td>0.0001</td>
<td>141±44</td>
<td>90±20</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV ESV, mL/m²</td>
<td>70±31</td>
<td>41±12</td>
<td>0.0001</td>
<td>75±35</td>
<td>44±15</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV effSV, mL/m²</td>
<td>41±11</td>
<td>47±7</td>
<td>0.024</td>
<td>40±9</td>
<td>44±10</td>
<td>0.061</td>
</tr>
<tr>
<td>RV EF, %</td>
<td>53±9</td>
<td>55±7</td>
<td>0.087</td>
<td>49±10</td>
<td>53±7</td>
<td>0.067</td>
</tr>
<tr>
<td>RV CO</td>
<td>3.1±0.9</td>
<td>3.6±0.7</td>
<td>0.005</td>
<td>2.9±0.7</td>
<td>3.1±0.8</td>
<td>0.244</td>
</tr>
<tr>
<td>LV EDV, mL/m²</td>
<td>62±11</td>
<td>74±13*</td>
<td>0.0001</td>
<td>69±10</td>
<td>73±13</td>
<td>0.049</td>
</tr>
<tr>
<td>LV ESV, mL/m²</td>
<td>23±8*</td>
<td>25±8</td>
<td>0.133</td>
<td>28±8</td>
<td>27±7</td>
<td>0.804</td>
</tr>
<tr>
<td>LV effSV, mL/m²</td>
<td>38±7</td>
<td>49±7*</td>
<td>0.0001</td>
<td>41±8</td>
<td>45±8</td>
<td>0.003</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>63±8</td>
<td>66±6</td>
<td>0.030</td>
<td>60±8</td>
<td>63±6</td>
<td>0.038</td>
</tr>
<tr>
<td>LV CO</td>
<td>2.9±0.6</td>
<td>3.7±0.7*</td>
<td>0.0001</td>
<td>3.0±0.6</td>
<td>3.2±0.6</td>
<td>0.046</td>
</tr>
<tr>
<td>RV/LV EDV</td>
<td>2.3±0.5</td>
<td>1.2±0.2</td>
<td>0.0001</td>
<td>2.1±0.6</td>
<td>1.3±0.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>PR, %</td>
<td>45±8*</td>
<td>7±8</td>
<td>0.0001</td>
<td>39±9</td>
<td>4±6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Statistical significance <0.05 (pre = at baseline, post = net change).

effSV indicates effective stroke volume; EDV, end diastolic volume; ESV, end systolic volume.

Figure 4. Box and whisker plots: z-scored VE/VCO₂ values pre- (dark gray) and post- (light gray) PVR in Group 1 (≤17.5 years) and Group 2 (>17.5 years) z VE/VCO₂ is averaged for the 3 assumptions made for normal values.
to surgery in the younger patients. This analysis may bring into question the use of an RV end diastolic volume to select patients for PVR, in that the index end diastolic volume may not vary dramatically over the time course of the patient’s life, but that chronic exposure to pulmonary incompetence leads to a reduction in RV compliance, resulting in a less good response to surgery.

It could argue that the lifetime management of patients with free pulmonary incompetence should include RVOT revision in late childhood/early adulthood that would potentially reduce the risk of future detrimental events.1-3 In particular, reduction in RV dilatation and the continued effects of chronic pulmonary incompetence may reduce the risk of sudden arrhythmias, which may be secondary to QRS prolongation (associated with RV volume dilatation2,28), right atrial enlargement (secondary to RV dilatation and tricuspid incompetence), or potential RV fibrosis.27 Subsequent conduit dysfunction could then be treated percutaneously and, if possible, over the remainder of the patient’s lifetime.

Limitations
An important limitation of this study comes from the lack of normal values for Ve/VCO2 in patients younger than 20 years; we have attempted to overcome this limitation by performing 3 different analyses assuming that normal values should have been somewhere between the 3 extrapolations that we performed. Nevertheless, all methods gave the same results, suggesting that the analysis is robust enough.

Conclusions
A relatively aggressive PVR policy (end diastolic volume <150 mL/m2) leads to normalization of right ventricular volumes, improvement in biventricular function, and submaximal exercise capacity. Normalization of Ve/VCO2 (a parameter of submaximal exercise capacity that best reflects patients every day requirements) is most likely to occur when surgery is performed at an age ≤17.5 years. PVR in this younger age group is associated with better LV filling and CO after surgery than in older patients.

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Disclosures
C.v.D served as a consultant to Medtronic, Inc. P.B. and A.M.T. served as consultants to Medtronic, Inc. The remaining authors have nothing to disclose.

References


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