Adult Congenital Heart Disease

Pulmonary Valve Replacement in Adults Late After Repair of Tetralogy of Fallot: Are We Operating Too Late?
Judith Therrien, MD, FRCP(C), Samuel C. Siu, MD, FRCP(C), Peter R. McLaughlin, MD, FRCP(C), Peter P. Liu, MD, FRCP(C), William G. Williams, MD, FRCS(C), Gary D. Webb, MD, FRCP(C)
Toronto, Canada

OBJECTIVES
The purpose of this study is to evaluate right ventricular (RV) volume and function after pulmonary valve replacement (PVR) and to address the issue of optimal surgical timing in these patients.

BACKGROUND
Chronic pulmonary regurgitation (PR) following repair of tetralogy of Fallot (TOF) leads to RV dilation and an increased incidence of sudden cardiac death in adult patients.

METHODS
We studied 25 consecutive adult patients who underwent PVR for significant PR late after repair of TOF. Radionuclide angiography was performed in all at a mean of 8.2 months (±8 months) before PVR and repeated at a mean of 28.0 months (±22.8 months) after the operation. Right ventricular (RV) end-systolic volume (RVESV), RV end-diastolic volume (RVEDV) and RV ejection fraction (RVEF) were measured.

RESULTS
Mean RVEDV, RVESV and RVEF remained unchanged after PVR (227.1 ml versus 214.9 ml, p = 0.74; 157.4 ml versus 155.4 ml, p = 0.94; 35.6% versus 34.7%, p = 0.78, respectively). Of the 10 patients with RVEF $\leq 0.40$ before PVR, 5 patients (50%) maintained an RVEF $\leq 0.40$ following PVR, whereas only 2 out of 15 patients (13%) with pre-operative values, $>0.40$ reached an RVEF $\geq 0.40$ postoperatively (p < 0.001).

CONCLUSIONS
Right ventricular recovery following PVR for chronic significant pulmonary regurgitation after repair of TOF may be compromised in the adult population. In order to maintain adequate RV contractility, pulmonary valve implant in these patients should be considered before RV function deteriorates. (J Am Coll Cardiol 2000;36:1670–5) © 2000 by the American College of Cardiology

The hemodynamic effect of long-term left-sided valvular regurgitation on its recipient chamber is manifest by progressive left ventricular (LV) dilation with preserved ejection fraction until irreversible LV pump failure supervenes (1). The prognosis of medically treated patients with severe, chronic aortic regurgitation is dismal when the condition is associated with symptoms, atrial fibrillation, progressive LV dilation or diminished LV contractility (2,3). The potential for reversibility of LV dysfunction following aortic valve replacement depends on pre-operative LV function and dimension (4–8). Consequently, timing of surgical intervention in such patients, before irreversible contractile impairment and pump dysfunction supervene, is the essence of the decision-making process (4–8). Chronic, isolated severe pulmonary regurgitation (PR) has been shown to result in right ventricular (RV) dilation (9–11). In adults with repaired Tetralogy of Fallot (TOF) and chronic PR, RV dilation has been shown to correlate with an increased incidence of sudden cardiac death (12,13). Little is known, however, of the fate of the RV after pulmonary valve replacement (PVR) in such patients (14–16). The reversible nature of RV dysfunction remains to be established in these adults, and the issue of optimal timing for PVR needs to be addressed. The purpose of this study is to evaluate consecutive patients with PVR and to determine their outcome in reference to pre-operative status.

MATERIALS AND METHODS

Patient population. We conducted a retrospective study evaluating all consecutive patients older than 18 years of age who underwent PVR for PR late after repair of TOF and selected all patients that had a routine rest and exercise radionuclide angiogram (RNA) test performed at the University of Toronto Congenital Cardiac Center for Adults before and after PVR. We reviewed and recorded surgical data including initial palliative procedures, details of repair and PVR. Clinical status of patients before and after PVR was ascertained from hospital records. Clinical arrhythmia was defined as: 1) sustained atrial flutter/fibrillation or sustained ventricular tachycardia documented on a 12-lead electrocardiogram (ECG), Holter recording and electrocardiographic strips or 2) palpitations associated with syncope or near syncope in patients subsequently found to have sustained atrial flutter/fibrillation or ventricular tachycardia at electrophysiological testing. Sustained arrhythmia was
defined as arrhythmia lasting >30 s or of any length if associated with symptoms other than palpitations.

**Echocardiographic analysis.** Pre-operative and postoperative (most recent) two-dimensional color Doppler and M-mode echocardiogram reports were reviewed on each patient. The severity of PR was assessed by pulse-wave Doppler characteristics and color flow mapping as previously described (17) and was graded as mild, moderate, or severe. Tricuspid regurgitation was also assessed according to standard technique. Right ventricular dilation was estimated from RV inlet measurements, made at end-diastole from apical four-chamber views (18). Right ventricular enlargement was considered mild when the RV inlet measured between 40 mm and 50 mm; moderate, between 50 mm and 60 mm; and severe, >60 mm.

**Surgical technique.** Pulmonary valve replacement was performed through a median sternotomy using standard cardiopulmonary bypass and mild systemic hypothermia (32° and 35°C) in all patients. Bioprosthetic pulmonary valves were sewn into the pulmonary annulus and covered with a patch of autologous pericardium. The pericardial patch extended from the pulmonary artery bifurcation onto the RV infundibulum.

**Radionuclide angiogram.** Radionuclide angiogram was performed at rest and maximal exercise before and after PVR. The patients were radio-labeled with Tc-99m with standard technique, and the patient was imaged supine using the standard views, including the best septal view that optimized separation of the RV from surrounding structures, including the LV and the left atrium. Right ventricular end-systolic-/diastolic volume (RVESV/RVEDV) and ejection fraction were calculated using semi-automated edge detection algorithm by two experienced technologists who were unaware of the patient’s clinical status. A right ventricular ejection fraction (RVEF) ≥0.40 was considered normal (19). Exercise testing was performed on a Quinton bicycle with gradual increase in the workload every 3 min until exhaustion or symptom development.

**Statistical analysis.** We analyzed the data using SPSS for Windows (version 7.0, SPSS, Chicago, Illinois). Descriptive data for continuous variables are presented as means ± SD or as medians with ranges, when appropriate. Discrete variables were analyzed by the chi-square or Fisher exact test. Continuous data were analyzed by the Wilcoxon rank-sum test. Pairwise analysis of continuous variables was performed using the Wilcoxon sign-rank test.

### RESULTS

**Patient population.** Four hundred sixty-five patients had repaired TOF, of which 55 underwent PVR as adults. Twenty-five patients (14 male and 11 female) had undergone rest and exercise RNA before and after PVR. Routine RNA testing became standard practice at our institution only during the last five years, explaining the relatively small percentage. Seventeen patients (68%) had one or more palliative procedures prior to intracardiac repair, most commonly a Blalock–Taussig shunt (52%). Mean age at TOF repair was 12.1 years (±10.6 years, range 4 to 43 years). A trans-RV approach at the time of repair was used in all patients, and a transannular patch was used in 44% of the patients. Indications for PVR were significant pulmonary regurgitation with either 1) exercise intolerance, 2) progressive RV dilation (identified from serial transthoracic echocardiographic studies), or 3) clinical arrhythmia, with most patients (56%) fulfilling two or three criteria (Table 1). Incidence of clinical arrhythmia was 20% in our patients’ cohort. One patient had concomitant moderate/severe RV outflow tract obstruction (Doppler gradient >50 mm Hg). PVR. Pulmonary valve replacement was performed at a mean age of 33.9 years (±9.2 years, range 19 to 53 years) with a mean time from repair to PVR of 21.8 years (±8.2 years, range 10 to 36 years). Most patients (96%) received a xenograft pulmonary valve, the size ranging from 25 to

### Table 1. Demographic and Surgical Characteristics: Total Cohort of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Prior palliation</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>BT shunt</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Mean age at initial repair, years</td>
<td>12.1 ± 10.6</td>
</tr>
<tr>
<td>Mean age at PVR, years</td>
<td>33.9 ± 9.2</td>
</tr>
<tr>
<td>Mean time from repair, years</td>
<td>21.8 ± 8.2</td>
</tr>
<tr>
<td>Indication for PVR</td>
<td></td>
</tr>
<tr>
<td>Dyspnea + RV dilation</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>RV dilation + arrhythmia</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Dyspnea alone</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>RV Dilation alone</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Arrhythmia alone</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Additional procedure</td>
<td></td>
</tr>
<tr>
<td>Aneurysm resection</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Relief of infundibular stenosis</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>TV annuloplasty</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>ASD closure</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>VSD closure</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Atrial cryoablation</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Ventricular cryoablation</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

ASD = atrial septal defect; BT = Blalock Taussig; PVR = pulmonary valve replacement; RV = right ventricle; TOF = Tetralogy of Fallot; TV = tricuspid valve; VSD = ventricular septal defect.
from 1.60 to 0.13, compared with its own pre-operative value ranged widely, 0.08 to 0.65, mean 0.34 (range 0.08 to 0.65, mean 0.34). There was a mean change in RVEF of 0.05 after PVR, compared with 24% before PVR (p = 0.001). Transthoracic echocardiography, performed at a mean of 2.6 years, 2.3 years and 2.2 years after PVR, whereas patients showing deterioration in RVEF, RVEDV and RVESV had their test done at a mean of 2.6 years, 2.3 years and 2.4 years after PVR (p = 0.36, 0.87 and 0.92, respectively).

Correlation between pre-operative echocardiographic findings and RNA was poor for judging hypokinesis (r = −0.47) as well as for quantifying RV dilation (r = 0.45). Similarly, there was no correlation between symptomatic

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-PVR</th>
<th>Post-PVR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III/IV</td>
<td>(n = 25)</td>
<td>(n = 25)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR ≥ moderate</td>
<td>25 (100%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TR ≥ moderate</td>
<td>9 (36%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RVOTO ≥50 mmHg</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean duration (min)</td>
<td>5.5 ± 1.9</td>
<td>5.8 ± 2.5</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean external workload</td>
<td>476 ± 182</td>
<td>440 ± 166</td>
<td>0.58</td>
</tr>
<tr>
<td>Mean RVEF at rest</td>
<td>0.35 ± 0.13</td>
<td>0.34 ± 0.11</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean RVESV at rest (ml)</td>
<td>157.4 ± 95.6</td>
<td>155.4 ± 125.9</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean RVEDV at rest (ml)</td>
<td>227.1 ± 119</td>
<td>214.9 ± 138</td>
<td>0.74</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RVEDV = right ventricular end-systolic volume; RVESV = right ventricular end-diastolic volume; RVETO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation.

Survival

There was no peri-operative mortality. At the latest follow-up (mean follow-up time of 2.36 years, ±2.24 years) there was no late death.

Follow up clinical status. Functional and echocardiographic data are shown in Table 2. At the latest follow-up (mean of 2.36 years), none of the patients was in functional class III-IV after PVR, compared with 24% before PVR (p < 0.001). Transthoracic echocardiography, performed at a mean of 1.9 years after PVR, showed a reduction in the incidence of moderate-to-severe pulmonary regurgitation as well as tricuspid regurgitation (100% vs. 0%, p < 0.001; 36% vs. 0%, p < 0.001, respectively).

RADIONUCLIDE ANGIOGRAPH. Results of the RNAs are shown in Table 2. Radionuclide angiograms were performed in all patients within a mean of 8.2 months (±8 months) prior to PVR and repeated at a mean of 28.0 months (±22.8 months) after the operation. Right ventricular function at rest ranged from 0.12 to 0.57 (mean 0.35 ± 0.13) before operation. Following PVR, RVEF did not change significantly (range 0.08 to 0.65, mean 0.34 ± 0.11, p = 0.78) (Fig. 1). Change in an individual’s RVEF compared with its own pre-operative value ranged widely, from 1.60 to −0.52, with a mean of 0.09 ± 0.55. Patients with right ventricular outflow tract (RVOT) aneurysm had a mean pre-operative RVEF of 0.38 ± 0.13, compared with a mean pre-operative RVEF of 0.34 ± 0.12 in patients without RVOT aneurysm (p = 0.39). There was a mean change in RVEF of 0.05 ± 0.36 following concomitant RV aneurysm repair compared with a mean change in RVEF of 0.12 ± 0.65 in patients not needing concomitant aneurysmectomy (p = 0.79). Of the 10 patients (4 patients with RVOT aneurysm) with an RVEF ≥0.40 prior to PVR, 5 patients (50%) (3 patients with RVOT aneurysm) maintained an ejection fraction ≥0.40, whereas only 2 out of 15 patients (13%) with pre-operative values <0.40 reached an ejection fraction ≥0.40 postoperatively (p < 0.001).

Before the operation, RVESV at rest ranged from 42 ml to 449 ml (mean 157.4 ml ± 95.6) and did not change significantly after PVR (range 54 ml to 553 ml, mean 155.4 ml ± 125.9, p = 0.94) (Fig. 2). Similarly, after pulmonary valve implant, RVEDV did not change significantly (mean 227.1 ml ± 119 pre-operatively vs. mean 214.9 ml ± 138 postoperatively, p = 0.74) (Fig. 3). Time interval between PVR and postoperative RNA had no impact on the results. Patients with improvement in RVEF, RVEDV and RVESV had their test done at a mean of 1.9 years, 2.4 years and 2.3 years after PVR, whereas patients showing deterioration in RVEF, RVEDV and RVESV had their test performed at a mean of 2.6 years, 2.3 years and 2.4 years after PVR (p = 0.36, 0.87 and 0.92, respectively).

Correlation between pre-operative echocardiographic findings and RNA was poor for judging hypokinesis (r = −0.47) as well as for quantifying RV dilation (r = 0.45). Similarly, there was no correlation between symptomatic
improvement and amelioration of postoperative RV function ($r = 0.1$).

EXERCISE CAPACITY. Measurement of exercise capacity did not reveal any significant improvement. The mean duration of exercise pre-operatively was 5.5 min ± 1.9 and 5.8 min ± 2.5 postoperatively ($p = 0.38$). Before PVR, patients achieved a mean maximal external workload (maximal heart rate × maximal systolic blood pressure) of 476 ± 182 compared with 440 ± 166 following PVR ($p = 0.58$) (Table 2).

DISCUSSION

Pulmonary valve replacement in our study was performed successfully, with 0% mortality and no recurrence of significant PR at a mean follow up of 2.36 years. Subjective improvement in clinical symptoms was also recorded. Despite these seemingly encouraging results, however, our data demonstrate the lack of significant improvement in RV contractility and dimension following pulmonary valve implant in our adult cohort. Similarly, objective measures of exercise capacity failed to improve after surgery. The proportion of patients having a normal RV contractility post-operatively (ejection fraction ≥0.40) was significantly increased when pre-operative RVEF was ≥0.40 ($p < 0.001$).

RNA

The effect of PVR on RV volume and contractility in children and adolescents with significant pulmonary regurgitation late after repaired TOF has been previously studied (14–16). Bove et al. (15) reported on eight such patients. Pulmonary valve replacement, performed at a mean age of 14.6 years, resulted in improvement in RVEF as measured by RNA and a diminution in RV end-diastolic dimension as measured by M-mode echocardiography. Subjective improvement in exercise tolerance was also recorded, but no objective assessment was performed (15). Warner et al. (16) reported on 16 patients undergoing PVR at a mean age of 12 years. They recorded a significant reduction of RV end-diastolic dimension as measured by M-mode echocardiography, and some improvement in objective exercise tolerance in six patients (16). A more recent study by d’Udekem et al. (14) on 15 patients who underwent PVR at a median age of 13 years, revealed no significant improvement in RV end-diastolic diameter when measured by RNA but found a significant decrease in the mean ratio between the end-diastolic diameter of the RV and LVs. Objective measurement of exercise capacity was not performed (14). The data reported from these studies differed from our findings. We believe that two factors are responsible for these differences.

Measurement of RV dimension by M-mode echocardiography as reported by Bove et al. (15) and Warner et al. (16) is highly dependent on image quality and cursor position. Furthermore, because of the complex geometry of the RV, the precision and reproducibility of such measurement is highly variable, and consequently, reported results should be interpreted with caution (20,21). Preliminary data from another study on 70 adults with repaired TOF undergoing PVR conducted at our center, showed a significant decrease in RV dimension after pulmonary valve implant transthoracic when assessed by echocardiography (22). Right ventricular dimension, taken from a four-chamber view, was in retrospect perhaps an over-simplified way to assess a complex 3D cavity such as the RV (23). With increasing experience, RNA for evaluation of RVEF and volume allows better detection and quantification of impaired RV function and dilation patients (24–27) and has gained widespread acceptance and application.

When RNA was used by d’Udekem et al. (14) and Bove et al. (15) to assess RV dimension and contractility after PVR, positive results were reported (14,15). The patient population reported by the previous authors, however, was significantly younger at the time of PVR when compared with our cohort of adult patients (mean of 13.0 years vs. 33.9 years, respectively). The potential for contractile recovery and ability of the RV to undergo remodeling after PVR may diminish over time. Perhaps the effect of chronic cyanosis (28), lack of adequate myocardial protection during cardiopulmonary bypass and direct myocardial damage from right ventriculotomy at the time of initial repair (29–31).
may impair the ability of the aging RV to recover after pulmonary valve implant. Alternatively, one may argue that RV recovery is simply slower in the adult population. This, however, is rather unlikely considering that LV recovery has been shown to occur well within one year of surgery in adult patients undergoing left-sided valvular surgery for chronic regurgitant lesions (11,32).

**EXERCISE CAPACITY**

The improvement in clinical symptoms reported by us and others was not substantiated by objective measurement of maximal exercise capacity performed in our study. This may not come as a surprise, as the subjective symptoms may improve because of a decrease in pulmonary artery pulsatility and/or change in pulmonary compliance. Objective exercise improvement, however, is dependent on net change in forward cardiac output or change in peripheral muscle conditioning. Furthermore, exercise capacity has been shown to inversely correlate with RV dilation in patients with repaired TOF (33). Our exercise results do corroborate with our RV volumetric data.

**CLINICAL IMPLICATIONS**

Because RV dilation has been linked to the development of tachycardia and sudden cardiac death (12,13), it is imperative that we try to prevent or reverse the process of RV dilation in time. Our study would indicate that if one wishes to maintain a normal RVEF postoperatively, the optimal timing of PVR in the adult population may be before the RV function starts to deteriorate.

**STUDY LIMITATIONS**

Right ventricular size and contractility remain difficult to quantify with precision because of the complex geometry. Despite its widespread use and acceptance, RNA has some limitations in the assessment of the RV (34). Magnetic resonance imaging (MRI) is now emerging as the gold standard technique to assess RV size and function (35,36), but data on RV function obtained with this technique were not available in our patients’ cohort. A second limitation is the retrospective nature of the data, which did not capture the entire data set. Potential referral biases cannot be excluded, although a wide range of ventricular dimension and performance was represented in our data set. Lastly, data on VO₂ max would have been desirable for a more complete assessment of objective exercise capacity in our patients.

**CONCLUSIONS**

The potential for RV recovery after PVR for chronic significant PR after repair of TOF may be compromised in the adult population. In order to maintain adequate RV contractility, pulmonary valve implant in these patients should be considered before RV dysfunction ensues. A multicenter prospective study including MRI and VO₂ max measurements should be conducted, addressing the issue of optimal timing of PVR in this patient population.

**REFERENCES**


