Pulmonary Valve Replacement in Tetralogy of Fallot
Impact on Survival and Ventricular Tachycardia

David M. Harrild, MD, PhD; Charles I. Berul, MD; Frank Cecchin, MD; Tal Geva, MD; Kimberlee Gauvreau, ScD; Frank Pigula, MD; Edward P. Walsh, MD

Background—Pulmonary valve replacement (PVR) in repaired tetralogy of Fallot (TOF) reduces pulmonary regurgitation and decreases right ventricular (RV) dilation, but its long-term impact on ventricular tachycardia (VT) and mortality is unknown. This study aimed to determine the incidence of death and VT in TOF after PVR and to test the hypothesis that PVR leads to improvement in these outcomes.

Methods and Results—A total of 98 patients with TOF and late PVR for RV dilation were identified. Matched control subjects were identified for 77 of these patients; control subjects had TOF with RV dilation but no PVR. Matching was done by age (±2 years) and baseline QRS duration (±30 ms). No significant differences were found in age, QRS duration, type or decade of initial repair, age at TOF repair, or presence of pre-PVR VT between the 2 groups; limited echocardiographic and magnetic resonance imaging data showed no difference in left ventricular function but more RV dilation among PVR patients than control subjects. In the PVR group, 13 events occurred over 272 patient-years. No significant change in QRS duration was seen for any group. Overall 5- and 10-year freedom from death, VT, or both was 80% and 41%, respectively. In the matched comparison, no significant differences were seen in VT, death, or combined VT and/or death (P=0.32, P=0.06 [nearly favoring controls], and P=0.21).

Conclusions—This cohort experienced either VT or death every 20 patient-years. In a matched comparison with a similar TOF group, late PVR for symptomatic pulmonary regurgitation/RV dilation did not reduce the incidence of VT or death.

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Key Words: arrhythmia ■ pulmonary valve replacement ■ survival ■ tetralogy of Fallot

Surgical relief of right ventricular (RV) outflow tract obstruction in tetralogy of Fallot (TOF) often includes a transannular incision extending from the muscular infundibulum to the main pulmonary artery. Although the afterload to the right ventricle is reduced, the tradeoff is pulmonary valvar incompetence, long-term pulmonary regurgitation, and progressive RV dilation.1,2 Placement of a valved homograft conduit from the right ventricle to the pulmonary artery, an alternative solution, typically has the same long-term complications caused by progressive degradation in bioprosthetic leaflet tissue. RV dilation is associated with vulnerability to arrhythmia; repaired TOF patients are known to be at increased long-term risk of mortality.3–5 A potential solution to this problem is pulmonary valve replacement (PVR), with the goal of reversing the process of RV dilation.

Clinical Perspective p 451

As the population of patients with repaired TOF ages, a growing number of patients can be expected to have pulmonary regurgitation and RV dilation. The question of when to perform a PVR, and in whom, is becoming increasingly pressing.6–10 Clear guidelines to assist in this decision have proved difficult to identify.

The present study has 2 goals. The first is to characterize the incidence of death and ventricular tachycardia (VT) among all repaired TOF patients with RV dilation and late PVR performed at our institution. The second is to determine whether PVR in these patients is protective from these outcomes by retrospectively comparing this cohort to matched controls.

Methods

Inclusion Criteria

Patients were identified in the database maintained within the cardiovascular program at our institution. At the time of database review (early 2007), 112 TOF patients had undergone PVR for RV dilation. Of these patients, only those with PVR >5 years from their TOF repair were included to focus on the impact of long-term volume load on the RV (leaving 101 patients in the study group). In addition, those with significant confounding structural heart disease were excluded (3 patients with complete atrioventricular canal defect...
Descriptive and Baseline Data
Demographic, surgical, and electrophysiological data included age at review, type of initial TOF repair (transannular patch versus conduits), era of and age at TOF repair, time between TOF repair and PVR, presence of pre-PVR VT, decade of and age at PVR, and QRS duration at PVR (on the most recent ECG available occurring ≤1 year before valve replacement). The QRS duration was provided by the automated analysis performed by the General Electric Marquette Electronics mac5000 platform (Fairfield, Conn) and confirmed by manual inspection.

Baseline echocardiographic data included qualitative assessments of left ventricular (LV) and RV function and RV dilation on the latest evaluation before PVR (at most 3 years removed). Dysfunction or dilation was characterized as none, mild, moderate, or severe. Baseline magnetic resonance imaging (MRI) data were LV and RV ejection fraction (EF), pulmonary regurgitation fraction, and RV end-diastolic volume (indexed to body surface area), again at most 3 years before PVR.

Outcome Data
The primary outcome variables were death and sustained VT. The former was identified within the hospital database system, followed by a search of the Social Security Death index. The latter was signaled by a documented episode of spontaneous sustained VT (eg, cardiac arrest), concerning symptoms or Holter findings leading to electrophysiology study with inducible VT, implantable cardioverter-defibrillator implantation for VT, or sustained VT documented by appropriate implantable cardioverter-defibrillator discharge. For many of the analyses, a composite measure of death and/or VT was used.

Secondary outcome measures were change in QRS duration and change in echocardiographic and MRI indices listed above. For the former, the post-PVR QRS duration was taken from the last available ECG, occurring at least 1 month after valve replacement. Patients with a paced rhythm on either pre- or post-PVR ECG were excluded from this portion of the analysis. For the latter, data from the last available MRI or echocardiogram were used, again at least 1 month after PVR; only patients with both baseline and follow-up exams were included in this analysis.

Control Subjects
Control subjects were selected from the pool of patients in our database with repaired TOF, pulmonary regurgitation, and RV dilation but no PVR (879 patients). For each PVR patient, a paired control was identified in a 2-step fashion (Figure 1). First, potential control subjects were identified who were matched by age ≥2 years; they were ordered according to age similarity to the PVR patients. Then, within this group of prospects, the first patient satisfying the following criterion was selected: On an ECG within 1 year of the PVR, the QRS duration was within 30 ms of the PVR patient’s ECG (occurring at most 1 year before PVR).

Results
All PVR Patients
Patient Characteristics and Baseline Data
For the 98 PVR patients in the study cohort, Table 1 contains demographic, surgical, and baseline electrophysiological data. The earliest TOF repair for this patient cohort was in 1958. Eighteen patients (19.1%) had QRS duration >180 ms. During the period between 1997 and 2003, 6 selected cases included surgical cryoablation in the RV outflow tract as VT...
treatment or prophylaxis based on preoperative electrophysiological mapping (this intervention was not adopted as a routine part of PVR at our institution). The total time during which these patients were followed up at Children’s Hospital Boston is 1879 years, 272 after PVR (mean, 2.8 ± 4.3 years; median, 1.1 year; range, 1 month to 25 years).

Outcomes

Table 2 shows the prevalence of the outcome variables death and VT and the composite measure (death and/or VT) in the PVR population. The event incidence was 4.8 per 100 patient-years. No perioperative mortality occurred (the earliest patient death occurred 1.2 years after PVR). Figure 3 shows freedom from the primary outcome variables. Five- and 10-year measures of freedom from the composite outcome were 80% and 41%, respectively. Five of the 7 patients who had undergone intraoperative cryoablation experienced VT during follow-up.

For the 55 patients in whom nonpaced pre- and post-PVR ECG data were available, no significant change was seen in pre- versus post-PVR QRS duration: 157.7 ± 29.6 versus 154.3 ± 30.5 ms; \(P = 0.09\) (time from PVR to ECG: mean, 3.0 ± 2.6 years; median, 2.4 years; range, 1 month to 13.2 years).

Table 3 summarizes baseline and follow-up echocardiographic and MRI data. The qualitative echocardiographic data show a decrease in the degree of RV dysfunction and dilation. The MRI data show a substantial decrease in the percentage of pulmonary regurgitation and RV end-diastolic volume, with a suggestion of a trivial decrease in LV function but no change in RV function. The median times between PVR and evaluation were 6.5 years (range, 0.1 to 60.9 years) and 1.1 years (range, 0.5 to 7.3 years) for echocardiography and MRI, respectively. Overall, LV function was well preserved for the study group both before and after surgery.

PVR Patient/Control Pairs

Patient Characteristics and Baseline Data

Table 4 shows select demographic, surgical, electrophysiological, echocardiographic, and MRI characteristics of the 77 PVR/control pairs. A comparison of the 2 populations shows no significant differences in age at review; age, repair type, or decade at TOF repair; presence of pre-PVR VT; or baseline QRS duration. The qualitative echocardiographic data suggest no differences in LV function but an increased preva-
ence of RV dysfunction and dilation in the PVR group. By MRI, no difference is present in LV EF; a slightly decreased RV EF (borderline P value) and significantly higher RV end-diastolic volume are present in the PVR group.

Significant (moderate or greater) qualitative echocardiographic RV outflow tract obstruction was uncommon, occurring in 13% and 10% of PVR patients and control subjects, respectively (P=0.37).

The aggregate durations over which PVR patients/controls were followed up, including pre-PVR time, were 1418 and 1492 years, respectively, with median values of 17.3 years (range, 0.0 to 50.0 years) and 15.9 years (range, 0.6 to 53.9 years). For each group, the total post-PVR duration was 171.6 years, with a median of 1.4 years (range, 0.01 to 13.2 years) and a mean of 2.2 years (2.7 years).

### Table 3. Baseline and Follow-Up Qualitative Echocardiographic Measures and Quantitative MRI Indexes

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Baseline, n (%)</th>
<th>Last, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dysfunction (n=40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (27.5)</td>
<td>15 (37.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mild</td>
<td>16 (39.0)</td>
<td>19 (47.5)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (22.5)</td>
<td>2 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (10.0)</td>
<td>4 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>LV dysfunction (n=57)</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>None</td>
<td>43 (75.4)</td>
<td>41 (71.9)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>13 (22.8)</td>
<td>11 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (1.8)</td>
<td>3 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
<td>2 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>RV dilation (n=27)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>0 (0.0)</td>
<td>6 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3 (11.1)</td>
<td>11 (40.7)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (40.7)</td>
<td>6 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>13 (48.2)</td>
<td>4 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>Moderate</td>
<td>Mild</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI</th>
<th>Echocardiography parameters</th>
<th>Baseline, n (%)</th>
<th>Last, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV EF (n=36), %</td>
<td>Mean (SD)</td>
<td>46 (9)</td>
<td>45 (12)</td>
<td>0.34</td>
</tr>
<tr>
<td>LV EF (n=34), %</td>
<td>Mean (SD)</td>
<td>60 (8)</td>
<td>57 (9)</td>
<td>0.04</td>
</tr>
<tr>
<td>PR (n=20), %</td>
<td>Mean (SD)</td>
<td>51 (13)</td>
<td>7 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVEDVi (n=35), mL/m²</td>
<td>Mean (SD)</td>
<td>194 (71)</td>
<td>131 (45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PR indicates pulmonary regurgitation; RVEDVi, RV end-diastolic volume indexed to body surface area.

### Table 4. Comparison of Demographic, Surgical, Electrophysiological, Echocardiographic, and MRI Baseline Characteristics of PVR and Control Groups

<table>
<thead>
<tr>
<th>PVR</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age at review, y</td>
<td>25.5 (7.3–59.9)</td>
<td>25.8 (7.2–60.8)</td>
</tr>
<tr>
<td>TOF repair type, n (%)</td>
<td>TAP</td>
<td>Conduit</td>
</tr>
<tr>
<td>1950–1969</td>
<td>7 (9.1)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>1970–1979</td>
<td>23 (29.9)</td>
<td>18 (23.4)</td>
</tr>
<tr>
<td>1980–1989</td>
<td>26 (33.8)</td>
<td>31 (40.3)</td>
</tr>
<tr>
<td>1990–1999</td>
<td>21 (27.3)</td>
<td>23 (29.9)</td>
</tr>
<tr>
<td>Median (range) age at TOF repair, y</td>
<td>1.3 (0–27.1)</td>
<td>2.9 (0–28.4)</td>
</tr>
<tr>
<td>Pre-PVR VT, n (%)</td>
<td>6 (7.8)</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td>Median QRS duration at PVR, ms</td>
<td>158 (86–224)</td>
<td>148 (82–200)</td>
</tr>
</tbody>
</table>

### Table 5. PVR and Control Group Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PVR, n (%)</th>
<th>Control, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4 (5.2)</td>
<td>0 (0.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>VT</td>
<td>8 (10.4)</td>
<td>5 (6.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Death or VT</td>
<td>9 (11.7)</td>
<td>5 (6.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>68 (88.3)</td>
<td>72 (93.5)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

### Outcomes

Table 5 shows the incidence of the outcome variables for the PVR patient/control pairs during follow-up. Nine patients (12%) in the PVR group experienced an event during this time compared with 5 patients in the control group (7%). Per 100 patient-years, the incidence of an event was 5.3 and 2.9 for PVR patients and control subjects, respectively. For the PVR group, the median QRS durations among patients with death and/or VT compared with those with event-free survival were 177 ms (range, 134 to 216 ms) and 156 ms (range, 86 to 224 ms).
respectively \( (P=0.046) \). For the control group, these values were 174 ms (range, 88 to 200 ms) and 146 ms (range, 82 to 200 ms; \( P=0.01 \)).

Figure 4 compares these 2 groups. The Figure addresses freedom from VT, probability of survival, and freedom from the composite measure (death and/or VT). There are no significant differences between groups for any of these measures. Adjustment for age and baseline QRS duration does not affect these comparisons. With regard to survival, a benefit to nonintervention approaches significance.

Pre- and post-PVR nonpaced ECGs were available for 46 patient pairs. For the PVR group, the QRS duration mean±SD values were 160.8±25.0 and 156.9±26.7 ms, respectively; for the control subjects, they were 153.3±26.4 and 151.9±26.2 ms. Comparing PVR patients and controls showed no difference in baseline QRS duration \( (P=0.16) \), time between ECGs \( (P=0.27) \), and change in QRS duration \( (P=0.38) \).

**Discussion**

Most patients with repaired TOF are subject to RV volume overload as a consequence of pulmonary valvar incompetence. This chronic load leads to progressive RV dilation, which can be associated with substantial morbidity and even mortality. PVR is increasingly being used in these patients to treat pulmonary insufficiency.

It has been suggested that PVR is protective against the development of future ventricular arrhythmia. The degree to which RV remodeling after PVR may reduce the arrhythmogenic substrate, however, is unknown. The QRS duration has been viewed as a proxy for this process, with some reports showing a reduction in duration after PVR. There remain no published data demonstrating a clear survival benefit from PVR, however, with only 1 matched trial examining this outcome. In addition, the optimal timing for PVR remains undetermined.

The present series catalogs the entire experience of our center with PVR in TOF, looking specifically at long-term
survival and freedom from VT. These results are analyzed by comparing PVR patients with a similar cohort of TOF patients with pulmonary insufficiency in whom PVR had not been performed. The primary outcome variables of death and VT were chosen both for their clinical importance and for their readily identifiable nature in a retrospective fashion, minimizing missed instances of either.

Ninety-eight patients were included in the descriptive portion of the study. Our institutional preference for neonatal repair is reflected in the median age at TOF repair of 2.0 years (contrasting with recent reported European series). In children born since 1990, 15 of 19 had a full repair before 13 months of age. Nearly three quarters of the repairs used a transannular patch. The mean time from TOF repair to PVR was nearly 20 years. Six percent of the population undergoing PVR had documented presurgical VT. The number of PVRs performed during the decades at Children’s Hospital Boston has risen dramatically, with 80% of the total surgical volume occurring during the years 2000 to 2006. The median age at PVR was 21 years, with a somewhat prolonged mean QRS duration equal to 158 ms. Nineteen percent of patients had a QRS duration >180 ms, a number associated with increased risk of VT and sudden death.

The incidence of death, VT, or both was 4.8 events per 100 patient-years. The prevalence of all-cause mortality in this population, 6.1%, is similar to the rates of sudden cardiac death reported by other groups later after TOF repair without PVR. The 5- and 10-year measures of freedom from death, VT, or both, 80% and 41%, vary from those in another recent large series of 158 post-PVR patients; however, the 2 studies differ in both inclusion criteria and the definition of end-point events.

No significant change was found in QRS duration after PVR in our cohort. Postoperative changes in this measure may be complex; published reports have had variable findings from an overall reduction to a lengthening to a brief change in qualitative echocardiographic LV function. For example, had more RV dilation and slightly worse RV function than their paired control subjects. By MRI, a slightly lower RV EF was found in the PVR group compared with normal in the control subjects; by MRI, a slightly lower RV EF was found in the former than in the latter (borderline P value).

The incidence of death, VT, or both for the PVR and control populations per 100 patient-years was 5.2 and 2.9, respectively. The median QRS duration was longer for patients with events for both the PVR and control groups. For none of the outcome variables did the PVR group have an improved outcome compared with matched control subjects; for the survival outcome, these patients approached a trajectory that was worse. In addition, no difference was found in the change in QRS duration between the PVR and control populations during the course of the study, similar to another recent report.

These results suggest that in this population, PVR may not have led to long-term benefits of arrhythmia reduction from RV remodeling despite a reduction in LV size. These findings are not inconsistent with a growing body of literature suggesting that a “window of opportunity” for intervention exists beyond which, for example, restoration of normal RV dimensions becomes impossible.

**Study Limitations**

Three limitations should be mentioned. First, this study was a nonrandomized comparison of intervention and nonintervention, not a randomized controlled clinical trial; as such, PVR patients and their control subjects were imperfectly matched. The subpopulation of PVR patients with available MRI data, for example, had more RV dilation and slightly worse RV function than their paired control subjects. (LV function, however, a primary predictor of adverse outcomes, was well matched; in addition, for the entire patient cohort, no differences were found in many other predictors of future adverse outcomes.) Second, as a consequence of the disproportionate number of PVRs performed recently and the conservative definition used for the follow-up period, the median follow-up time is quite limited. It may be that a protective effect will not be seen until these patients are followed up longer. Third, these results make no comment on any beneficial impact that PVR might have on patients’ subjective symptomatology or objective exercise capacity.

**Conclusions**

In a large cohort of patients with repaired TOF and RV dilation at our institution, the incidence of death or sustained VT after PVR is considerable at 1 event per 20 patient-years. QRS duration did not change significantly after PVR over the course of the study. Compared with a group of similar control subjects, PVR did not result in improved survival or decreased incidence of VT. These data support continued efforts to refine the proper clinical indications and timing for referral to PVR in patients with repaired TOF.

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Disclosures
None.

References

CLINICAL PERSPECTIVE
Tetralogy of Fallot, the most common cyanotic congenital heart defect, combines a large ventricular septal defect with right ventricular outflow tract obstruction. In addition to closure of the ventricular septal defect, the traditional surgical repair for this lesion has included disruption of the pulmonary valve annulus with an outflow tract patch. The tradeoff for this very effective reduction in right ventricular pressure load is exposure of the right ventricular myocardium to a long-standing volume load from pulmonary regurgitation. Aging patients with repaired tetralogy of Fallot have been shown to be predisposed to exercise intolerance, arrhythmia, and premature death. Accordingly, a growing amount of attention is being paid to the potential impact of the chronic increase in right ventricular work to which these patients are exposed. Pulmonary valve replacement is an intuitively appealing means of addressing this problem. Pulmonary valve replacement has been shown to dramatically reduce the amount of pulmonary regurgitation and to lead to a reduced size of the right ventricular cavity. The risk-to-benefit calculus for this procedure, however, has not been well established. The present report uses a pair of retrospective matched cohorts to investigate the impact of pulmonary valve replacement on survival and ventricular tachycardia. In the cohorts studied, pulmonary valve replacement failed to reduce ventricular tachycardia or to prolong survival. These results serve as a cautionary tale; they may help to guide expectations after this surgery for the patient and physician alike. At a minimum, they support continued thoughtful and systematic investigations into the specific indications for and timing of pulmonary valve replacement.
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