Impact of Pulmonary Valve Replacement on Arrhythmia Propensity Late After Repair of Tetralogy of Fallot

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Background—Chronic pulmonary regurgitation after repair of tetralogy of Fallot (TOF) may lead to right ventricular dilatation, which may be accompanied by ventricular tachycardia and sudden death. We aimed to examine the effects of pulmonary valve replacement (PVR) on (1) certain electrocardiographic markers predictive of monomorphic ventricular arrhythmia and sudden death and (2) sustained atrial flutter/fibrillation and monomorphic ventricular tachycardia.

Methods and Results—We studied 70 patients who underwent PVR for pulmonary regurgitation and/or right ventricular outflow tract obstruction late after repair of TOF. Maximum QRS duration and QT dispersion were measured from standard ECGs before PVR and at the latest follow-up. Arrhythmia was defined as sustained atrial flutter/fibrillation or sustained monomorphic ventricular tachycardia. Comitant intraoperative electrophysiological mapping and/or cryoablation were performed in 9 patients (60%) with preexisting ventricular tachycardia and 6 patients (50%) with preexisting atrial flutter. QRS duration remained unchanged in the study group ($P=0.46$), but it was significantly prolonged ($P<0.001$) in a comparable group of patients with repaired TOF who did not undergo PVR. At a mean follow-up of 4.7 years, the incidence of ventricular tachycardia diminished from 22% to 9% ($P<0.001$), and atrial flutter/fibrillation decreased from 17% to 12% ($P=0.32$). Intraoperative ablation prevented recurrence of preexisting tachyarrhythmia (0 of 15 patients).

Conclusions—PVR in patients with previous TOF repair and chronic pulmonary regurgitation leads to stabilization of QRS duration and, in conjunction with intraoperative cryoablation, to a decrease in the incidence of preexisting atrial and ventricular tachyarrhythmia. When applicable, this combined approach should be used in patients late after repair of TOF. (Circulation. 2001;103:2489-2494.)

Key Words: pulmonary valve ■ ablation ■ tetralogy of Fallot ■ heart diseases

Intracardiac repair of tetralogy of Fallot (TOF) has been accomplished with success since the mid-1950s, with a favorable long-term outcome for the majority of patients.1–3 Chronic pulmonary regurgitation (PR), however, may be problematic and lead to right ventricular dilatation and exercise intolerance, and it may be accompanied by ventricular tachycardia and sudden death.4,5 Certain electrocardiographic markers, namely QRS prolongation6–9 and marked QT dispersion,9 correlate with right ventricular dilatation and are predictive of sustained monomorphic ventricular tachycardia and sudden death. Pulmonary valve replacement (PVR) in patients with substantial PR and impaired right-sided hemodynamics after TOF repair can be performed safely10 and results in a reduction of right ventricular dilatation and improved right ventricular function and exercise tolerance.11–13 However, little is known about the possible effects of PVR on some electrocardiographic predictors of monomorphic ventricular tachycardia and sudden death and on the fate of atrial flutter/fibrillation and ventricular tachycardia after PVR. We hypothesized that restoration of pulmonary valve competence with pulmonary valve implantation and reduction of PR may lead to stabilization or reduction of QRS duration and QT dispersion with a corresponding decrease in arrhythmia (namely, monomorphic ventricular tachycardia and atrial flutter/fibrillation).

Methods

Patient Population
From the databases of 4 participating hospitals, we identified all consecutive patients older than 18 years of age who underwent PVR for PR and/or right ventricular outflow tract obstruction late after repair of TOF. Twenty-eight patients (40%) were reported in previous studies.14–16 We reviewed and recorded surgical data,
including initial palliative procedures, details of repair, and PVR. The clinical status of patients before PVR was ascertained from hospital records. Current or latest status of patients was assessed from clinic visits and patient or physician contact. Death and late sustained atrial flutter/fibrillation or sustained monomorphic ventricular tachycardia after PVR were the clinical end points of the study.

Echocardiographic Analysis
Preoperative and postoperative (most recent) 2D color Doppler and M-mode echocardiograms, obtained using different commercially available machines, were reviewed for each patient. The severity of the PR was assessed by pulse-wave Doppler characteristics and color flow mapping, as previously described,17 and it was graded as mild, moderate, or severe. Degree of right ventricular outflow tract obstruction was derived from the peak velocity of the right ventricular outflow tract obtained by continuous Doppler (P=a4V where P indicates pressure and V, velocity). Right ventricular dilatation was estimated from right ventricular inlet measurements made at end-diastole from apical 4-chamber views.18 Right ventricular enlargement was considered mild when the right ventricular inlet measured between 40 and 50 mm, moderate when it was between 50 and 60 mm, and severe when it was >60 mm.

Electrocardiographic Measurements
Preoperative (baseline) and late postoperative (most recent) electrocardiographic parameters (RR interval, QRS duration, and QT dispersion) were analyzed manually by a cardiologist who was blinded to clinical data. Standard (speed, 25 mm/s and 1 mV/cm standardization) resting 12-lead ECGs were used. QRS duration was defined as the maximal QRS length in any lead from the first inflection to the final sharp vector crossing the isoelectric line. QT interval was considered as the maximal QT interval minus the minimal QT interval in any of the 12 leads. QT interval was measured from the first inflection of the Q wave to the final sharp vector of the T wave crossing the isoelectric line. U waves were not included in the QT interval measurement when prominent (U wave >50% of T wave or biphasic).6–9 Serial ECGs of 30 patients (control group) with repaired tetralogy and moderate to severe PR who had not undergone PVR by the study’s end (matched for age at repair and length of follow-up with the patients who had PVR) were analyzed in a similar manner.

Arrhythmia
Significant arrhythmia was defined as (1) sustained atrial flutter/fibrillation or sustained monomorphic ventricular tachycardia documented on a 12 lead-ECG, Holter recording, or electrocardiographic strips or (2) palpitations associated with syncope or near syncope in patients who were subsequently found to have inducible sustained atrial flutter/fibrillation or sustained monomorphic ventricular tachycardia at electrophysiological testing. Sustained was defined as arrhythmia lasting >30 seconds or of any length of time if associated with hemodynamic compromise. Atrial flutter/fibrillation and monomorphic ventricular tachycardia were classified as preoperative (ie, occurring before PVR) and late postoperative (ie, occurring after the first 3 postoperative months from PVR). The need for antiarrhythmic medication preoperatively and at the latest follow-up was also recorded for each patient.

Surgical Technique
PVR was performed through a median sternotomy using standard cardiopulmonary bypass and mild systemic hypothermia (32°C and 35°C). 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 to the right ventricular infundibulum.

Intraoperative Cryoablation
The objective of ventricular and atrial cryoablation was to identify and eliminate an area of slowed conduction responsible for a reentry circuit, which is thought to be a necessary substrate for monomorphic ventricular tachycardia and atrial flutter, respectively, in this patient population.

Monomorphic Ventricular Tachycardia
Intraoperative electrophysiological mapping was performed in one center as previously described17,20 using a customized right ventricular balloon electrode array for recording endocardial activation along with a sock positioned over the surface of the heart for epicardial recording. This enabled the simultaneous recording of endocardial and epicardial activation from 224 sites using a multiplex recording system.20 Induction of ventricular tachycardia was performed using a standard pacing protocol from the right ventricular apex. After induction and mapping, ventricular cryoablation was performed over the critical areas using a 1 cm tip cryoprobe applied down to −60°C for 2 minutes at a time.

Atrial Flutter
At the same center, for those patients with documented atrial flutter preoperatively, intraoperative atrial cryoablation was performed using a similar technique. The cryoprobe was applied in a serial manner between the inferior vena cava orifice and the tricuspid annulus.

Statistical Analysis
We analyzed the data using SPSS for Windows (version 7.0). Descriptive data for continuous variables are presented as mean±SD or as medians with ranges, when appropriate. Discrete variables were analyzed by χ2 or Fisher’s exact tests. Comparisons of continuous data between study and control groups were performed using 2-sample t tests or the Wilcoxon rank-sum test, wherever appropriate. Pair-wise comparisons of continuous variables within each group were performed using a paired t test or Wilcoxon sign rank test. The probability of survival and freedom from preexisting sustained atrial flutter/fibrillation or monomorphic ventricular tachycardia over time is displayed with Kaplan-Meier plots.

Results
Patients
A total of 70 patients, 33 male (47%) and 37 female (53%), fulfilled entry criteria. Forty patients (60%) had ≥1 palliative procedure before intracardiac repair, most commonly a Blalock-Taussig shunt (48%). Median age at TOF repair was 7.0 years (range, 1 to 40 years). A transannular patch was used in 39% of the patients (Table 1). Before PVR, 12 patients (18%) were in New York Heart Association (NYHA) functional class III or IV. Twelve patients (17%) had experienced atrial flutter/fibrillation, and 15 patients (22%) had monomorphic ventricular tachycardia at a median time of 4 years (range, 6 weeks to 24 years) before PVR. Indications for PVR were (1) exercise intolerance, (2) progressive right ventricular dilatation (identified from serial transthoracic echocardiographic studies), and (3) clinical arrhythmia, with most patients (55%) fulfilling 2 or 3 criteria. Four patients had isolated moderate-to-severe right ventricular outflow tract obstruction (peak Doppler gradient >50 mm Hg) without substantial PR. The control group was composed of 30 adult patients (18 men) with previous tetralogy repair and moderate-to-severe PR. Their surgical data are presented in Table 1. The control group only differed from the study group in that they had not undergone PVR by the study end. The mean time from repair to the study baseline ECG was 18.1 years for the study group versus 21.1 years in the control group.
Pulmonary Valve Replacement

PVR was performed at a median age of 28.2 years (range, 9.6 to 53.9 years), with a median time from repair to PVR of 16.8 years (range, 3 to 36 years). Most patients (86%) received a xenograft pulmonary valve; the valve size ranged from 21 to 34 mm. Additional procedures performed at the time of PVR are listed in Table 1.

Survival

There were 3 perioperative deaths for an operative mortality of 4%. Two deaths were due to multiorgan failure, and one was due to intractable right-sided congestive heart failure. All 3 patients had severe PR and severe right ventricular enlargement at the time of PVR. At 3 and 9 years after PVR, 2 more patients died. Death was due to right-sided heart failure in one patient and sudden death, presumably arrhythmic, in the other. The latter patient did not have ventricular arrhythmia preoperatively but had undergone residual ventricular septal defect closure through a left ventriculotomy and, subsequently, had developed biventricular failure with a hemodynamically significant residual ventricular septal defect and intermittent right-sided monomorphic ventricular tachycardia. Probability of survival after PVR was 92% at 5 years and 86% at 10 years (Figure 1).

Current Status

Functional and Hemodynamic Data

Functional and hemodynamic data are shown in Table 2. At the latest follow up, only 6% of patients were in NYHA functional class III to IV after PVR compared with 18% before PVR ($P=0.009$). Moderate-to-severe right ventricular dilatation, as assessed by transthoracic echocardiography, was also decreased by study end to 37% of patients compared with 71% preoperatively ($P<0.001$).

Electrocardiographic Markers

ECG measurements are shown in Table 2. At a mean of 4.7 years from PVR, mean QRS duration remained unchanged (mean of 178 ms preoperatively to 176 ms at latest follow-up; $P=0.46$; Figure 2). QT dispersion likewise remained unchanged after PVR. In contrast, mean QRS duration prolonged significantly (from 171 ms to 181 ms; $P<0.001$; Figure 2) over a similar length of follow up (4.9 years) in the control group of repaired tetralogy patients who had not undergone PVR by the study end. QT dispersion in the control group, like the group with PVR, remained unchanged.

**TABLE 1. Demographic and Surgical Characteristics of Total Cohort of Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group (n=70)</th>
<th>Control group (n=30)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>33 (47)</td>
<td>18 (60)</td>
<td>0.28</td>
</tr>
<tr>
<td>Prior palliation</td>
<td>40 (60)</td>
<td>14 (46)</td>
<td>0.39</td>
</tr>
<tr>
<td>BT shunt</td>
<td>34 (48)</td>
<td>14 (46)</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean age at repair, y</td>
<td>9.7±8.2</td>
<td>9.4±8.0</td>
<td>0.87</td>
</tr>
<tr>
<td>TAP</td>
<td>27 (39)</td>
<td>14 (46)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean age at PVR, y</td>
<td>27.8±11.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time from repair, y</td>
<td>18.1±8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm resection</td>
<td>33 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relief infundibular stenosis</td>
<td>16 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary arterioplasty</td>
<td>17 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV annuloplasty</td>
<td>9 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closure of residual shunts</td>
<td>9 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryoablation—atrial</td>
<td>6 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryoablation—ventricular</td>
<td>9 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA maze</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative death</td>
<td>3 (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). BT indicates Blalock Taussig; TAP, transannular patch used for right ventricular outflow tract reconstruction; TV, tricuspid valve; and RA, right atrium.

**TABLE 2. Clinical, Hemodynamic, and Electrocardiographic Data Before and at the Latest Clinical Review After PVR**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before PVR</th>
<th>After PVR</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>n=70</td>
<td>n=67</td>
<td></td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>12 (18)</td>
<td>4 (6)</td>
<td>0.009</td>
</tr>
<tr>
<td>SVT or VT</td>
<td>27 (39)</td>
<td>14 (21)</td>
<td>0.005</td>
</tr>
<tr>
<td>VT</td>
<td>12 (17)</td>
<td>8 (12)</td>
<td>0.32</td>
</tr>
<tr>
<td>Antiarrhythmic medication</td>
<td>14 (20)</td>
<td>11 (16)</td>
<td>0.58</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>n=65</td>
<td>n=55</td>
<td></td>
</tr>
<tr>
<td>PR≥moderate</td>
<td>60 (92)</td>
<td>11 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TR≥moderate</td>
<td>25 (37)</td>
<td>12 (22)</td>
<td>0.03</td>
</tr>
<tr>
<td>RVSP≥2/3 systemic pressure</td>
<td>12 (19)</td>
<td>1 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV dilatation≥moderate</td>
<td>47 (71)</td>
<td>20 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECG</td>
<td>n=61</td>
<td>n=54</td>
<td></td>
</tr>
<tr>
<td>RR, ms</td>
<td>800±110</td>
<td>836±214</td>
<td>0.32</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>178±30</td>
<td>176±24</td>
<td>0.46</td>
</tr>
<tr>
<td>QT dispersion, ms</td>
<td>105±50</td>
<td>110±49</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). NYHA indicates New York Heart Association; PR, pulmonary regurgitation; RR, RR interval; RV, right ventricular; RVSP, right ventricular systolic pressure; SVT, supraventricular tachycardia; TR, tricuspid regurgitation; and VT, ventricular arrhythmia.
Arrhythmias
The incidence of monomorphic ventricular tachycardia decreased from 22% preoperatively to 9% postoperatively \((P<0.001)\). Atrial flutter/fibrillation decreased from 17% preoperatively to 12% postoperatively \((P=0.32; \text{Figure 3})\).

Role of Cryoablation
Of the 15 patients with monomorphic ventricular tachycardia preoperatively, 9 patients underwent concomitant intraoperative mapping and ventricular cryoablation at the time of pulmonary valve implant. Postoperatively, none of them had recurrent ventricular tachycardia, whereas 2 of 6 patients who had not undergone ventricular cryoablation at the time of surgery had recurrent monomorphic ventricular arrhythmia \((P<0.001)\). Of the 12 patients with atrial flutter/fibrillation before surgery, 6 underwent atrial cryoablation at the time of pulmonary valve implant. All 6 patients remained free of atrial tachyarrhythmia at follow-up, whereas 4 out of 6 patients who had not undergone atrial cryoablation had recurrent atrial flutter at follow-up \((P<0.001)\).

Freedom from preexisting atrial flutter/fibrillation or ventricular tachycardia was 100% at 5 years in patients with concomitant intraoperative cryoablation compared with 68% at 5 years in patients receiving no concomitant cryoablation at the time of PVR \((P=0.055; \text{Figure 4})\). One patient who underwent cryoablation for monomorphic ventricular tachycardia subsequently developed supraventricular tachycardia after PVR.
Discussion
This study provides, for the first time, evidence that PVR late after TOF repair has a stabilizing effect on QRS duration and, in conjunction with intraoperative cryoaiblation, leads to a decrease in the incidence of preexisting atrial and ventricular tachyarrhythmia.

Mortality
PVR has been performed with a low operative mortality of 2% and a reported 10-year survival rate of 92% to 95%. Perioperative mortality in the present multicenter study was 4%, with a 10-year survival of 86%. Patients from our series were older at the time of PVR than in the previous series (mean age, 27.8 years versus 17.4 years). All patients who suffered perioperative death in our study had established advanced right ventricular dysfunction, suggesting that delayed PVR may have contributed to poor outcome.

Functional Status
Functional status improved after PVR, with a concomitant decrease in right ventricular dilatation as assessed by trans-thoracic echocardiography. Our data are in accord with previous published reports by Warner et al and Bove et al but in some disagreement with recent data published by our group regarding the effect of PVR on right ventricular volume. Younger age at PVR in this larger cohort of patients from the present study, as well as the use of echocardiography, at best a semiquantitative method of measuring right ventricular size, may explain the differences observed.

ECG Markers
QRS duration after PVR remained stable at a mean follow-up of 4.7 years. In contrast, there was a significant interval increase in QRS duration in the control group. The data from the present study are in accord with our recent longitudinal report of 793 adults with repaired TOF in whom QRS duration increased by an average of 2 ms per year for the whole group. QRS prolongation after repair of TOF reflects abnormal and delayed ventricular depolarization and correlates with the degree of right ventricular dilatation. Furthermore, a QRS duration >180 ms is a sensitive predictor of sudden death. The QRS prolongation observed in our control group suggests progressive right ventricular dilatation in this group of patients with repaired TOF and moderate to severe PR but no PVR. This is analogous to the effect of chronic left-sided regurgitant lesions on their recipient ventricular chambers. Stabilization of the QRS complex in the study group would suggest stabilization of right ventricular volume or alternatively, according to our echocardiographic data, a reduction in right ventricular volume counteracted by further “damage” of the conduction tissue at the time of PVR (aneurysm plication, infundibulectomy, closure of residual ventricular septal defect), leading to an overall stabilization of QRS complex to preoperative baseline levels.

Reduction in Arrhythmias
A significant reduction in the incidence of preexisting monomorphic ventricular tachycardia after PVR was observed. Furthermore, patients undergoing concomitant cryotherapy for ventricular or atrial arrhythmia had a greater chance to remain arrhythmia-free over time (P=0.055). Given the clearly divergent curves on Figure 4, we think that statistical significance (P<0.05) was not reached in this analysis because of the relatively small group size. A similar trend was previously suggested by the work of Oechslin et al and Harrison et al.

Right ventricular enlargement from chronic PR is a common hemodynamic substrate in patients with repaired TOF who develop sustained monomorphic ventricular tachycardia. It is thought that right ventricular myocardial stretch engenders areas of inhomogeneous electrical activity, predisposing to the development of ventricular arrhythmia. Right ventricular scar tissue from prior ventriculotomy, however, may provide areas of slowed ventricular activation, further facilitating the development of reentry. Similarly, right atrial dilatation from volume or pressure load prolongs atrial refractoriness in a heterogeneous manner. This dilatation, together with right atrial scarring from previous surgery, makes the atria susceptible to reentrant arrhythmia. Our data suggest that to abolish preexisting arrhythmias, ventricular or supraventricular, a combined approach is needed that addresses not only cavity dilatation but also focuses on the arrhythmia (the areas of slowed conduction) with concomitant cryotherapy.

Longevity of Pulmonary Valve Prosthesis
The average life span of a bioprosthesis or homograft pulmonary valve varies from 7 to 15 years. The need for repeat pulmonary valve surgery in these patients is a cause of concern. It may be that different valves, such as single-disk mechanical prostheses, which were recently shown to be safe and less thrombogenic than previously thought, will eliminate the need for multiple operations in the right ventricular outflow tract for these patients. This is speculative, however. At present, preservation of right ventricular function with PVR has to be weighed against possible further cardiac surgery.

Limitations of the Study
Our study reports on an intention-to-treat cohort and therefore cannot directly answer the question of whether PVR with or without cryotherapy should be performed in all patients with previous repair of TOF and similar hemodynamics. Selection criteria for PVR in the study were clinically determined, and we think they are representative of current practice for adults with repaired TOF. Previous aortopulmonary shunts in patients with tetralogy repair and long-standing left heart volume overload may also lead to arrhythmia originating from the left side. The principal focus of our study, however, was on the right ventricle and its well-documented potential to develop sustained ventricular tachycardia. Larger scale, prospective studies with complete datasets may clarify the role of PVR in adult survivors of tetralogy repair.

Conclusions
We showed that in patients with repaired TOF and progressive right ventricular dilatation, exercise intolerance, symp-
omatic atrial flutter/fibrillation, or monomorphic ventricular tachycardia, PVR leads to a stabilization of QRS duration. Furthermore, PVR in these patients, when combined with intraoperative cryoablation, leads to a decrease in the incidence rate of preexisting atrial and ventricular tachyarrhythmias. When applicable, this combined approach should be used in patients late after TOF repair.

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