Ventricular Arrhythmia Risk Stratification in Patients With Tetralogy of Fallot at the Time of Pulmonary Valve Replacement

Anna Sabate Rotes, MD; Heidi M. Connolly, MD; Carole A. Warnes, MD; Naser M. Ammash, MD; Sabrina D. Phillips, MD; Joseph A. Dearani, MD; Hartzell V. Schaff, MD; Harold M. Burkhart, MD; David O. Hodge, MS; Samuel J. Asirvatham, MD; Christopher J. McLeod, MBChB, PhD

Background—Most patients with repaired tetralogy of Fallot require pulmonary valve replacement (PVR), but the evaluation for and management of ventricular arrhythmia remain unclear. This study is aimed at clarifying the optimal approach to this potentially life-threatening issue at the time of PVR.

Methods and Results—A retrospective analysis was performed on 205 patients with repaired tetralogy of Fallot undergoing PVR at our institution between 1988 and 2010. Median age was 32.9 (range, 25.6) years. Previous ventricular tachycardia occurred in 16 patients (8%) and 37 (16%) had left ventricular dysfunction, defined as left ventricular ejection fraction <50%. Surgical right ventricular outflow tract cryoablation was performed in 22 patients (10.7%). The primary outcome was a combined event including ventricular tachycardia, out-of-hospital cardiac arrest, appropriate implantable cardioverter defibrillator therapy, and sudden cardiac death. Freedom from the combined event at 5, 10, and 15 years was 95%, 90%, and 79%, respectively. In the first year after PVR, 2 events occurred. Conversely, in the 22 patients who underwent surgical cryoablation, a single event occurred 7 years after PVR. A history of ventricular tachycardia and left ventricular dysfunction was associated with higher risk for the combined event (hazard ratio, 4.7; P=0.004 and hazard ratio, 0.8; P=0.02, respectively).

Conclusions—Patients with repaired tetralogy of Fallot undergoing PVR with history of ventricular tachycardia or left ventricular dysfunction appear to be associated with a higher risk of arrhythmic events after operation. Events in the first year after PVR are rare, and in select high-risk patients, surgical cryoablation does not seem to increase arrhythmic events and may be protective. (Circ Arrhythm Electrophysiol. 2015;8:110-116. DOI: 10.1161/CIRCEP.114.001975.)

Key Words: arrhythmias, cardiac ■ cryosurgery ■ heart valve prosthesis implantation ■ pulmonary valve ■ tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect and is typically repaired with low risk and excellent long-term results.1-3 Most patients however do require pulmonary valve replacement (PVR) later in life. To date, there is not a consistent approach in the determination and management of sudden cardiac death (SCD) risk at the time of PVR. The clinical use of pre-emptive preoperative electrophysiological study (EPS) and surgical cryoablation at the time of open repair is not agreed on,4-6 but is common in practice. Despite programmed ventricular stimulation being of diagnostic and prognostic value,7 the appropriate timing of EPS has not been studied.

Before PVR for severe pulmonary regurgitation in TOF, the volume loaded and dysfunctional right ventricle (RV) is vulnerable to ventricular arrhythmia;8 conceptually, PVR can reverse the volume overload and potentially mitigate against the development of ventricular tachycardia (VT). Intracardiac mapping and ablation, however, have confirmed that the VT is typically of a macroreentrant nature using the cardiac valves and ventricular scars as boundaries,6,7 and therefore surgical ablation of the RV outflow tract (RVOT) presents a logical approach to isolate diseased substrate.5,9,10

This study is aimed at clarifying the optimal approach to ventricular arrhythmia management in TOF patients at the time of PVR, by highlighting (1) novel predictors of ventricular arrhythmia, (2) whether EPS is of clinical use, (3) identify the most suitable time to perform the EPS for risk stratification, and (4) whether RVOT cryoablation is of clinical use.
WHAT IS KNOWN

- Sudden cardiac death (SCD) secondary to ventricular tachycardia is the most common cause of death in adults with repaired tetralogy of Fallot.
- Replacement of the pulmonary valve is frequently required later in life after the initial repair, but it does not reduce the risk of SCD.
- Pulmonary valve does, however, present an important opportunity for risk stratification against SCD, and the optimal approach is debated.

WHAT THE STUDY ADDS

- Left ventricular dysfunction is a significant predictor of SCD or appropriate implantable defibrillator therapies in this group.
- Open empirical cryoablation at the time of pulmonary valve replacement seems to be safe and may be protective.
- SCD is rare in the year after pulmonary valve replacement, and risk-stratifying electrophysiological testing can be delayed.

Methods

Population
A total of 537 consecutive patients with the diagnosis of TOF had 641 surgeries between October 1988 and December 2010 in Mayo Clinic, Rochester, MN. From those, 205 patients with TOF who had undergone previous complete repair and had reoperation to restore pulmonary valve function were selected. All reoperations were performed at this institution, but some initial repairs were undertaken elsewhere. Patients with concomitant pulmonary atresia, absent pulmonary valve, atrioventricular canal, and previous conduit or PVR were excluded. The study was approved by the Mayo Clinic Institutional Review Board, and all patients provided consent for their data to be used for study purposes.

Descriptive and Baseline Data
Medical history, perioperative, and follow-up data were collected using all available records.

An ECG at the time of PVR was available for all patients. Electrocardiograms were analyzed by an independent observer who was blinded to the clinical outcome of each patient (C.J.M.).

The criteria used for QRS fragmentation are well validated for other forms of cardiac disease, and the ECG phenotype was broken into (1) notched QRS, (2) fragmented QRS, or (3) normal ECG.

Holter monitoring before the PVR was available in 46 patients (22%). The degree of ectopy was graded following the Lown criteria, although modified as described: 0, no ventricular ectopic beats; 1, occasional, isolated ventricular premature beats (VPBs); 2, frequent VPB (>1/min or 30/h); 3, multiform VPB; 4, repetitive VPB (a) couplets, (b) salvos; ≥3 VPBs; 5, VT (>30 seconds). Nonsustained VT was defined as ≥4 consecutive ventricular beats documented on a 12-lead ECG, Holter recording, or ECG strips, lasting ≤30 seconds.

High risk for arrhythmia was considered when patients had documented sustained VT, unexplained syncope, QRS duration ≥180 ms, prior ventriculotomy, documented nonsustained VT or left ventricular (LV) dysfunction. Indications for performing an EPS before surgery include unexplained syncope or near syncope and nonsustained VT on Holter. Indications for implantable cardioverter defibrillator (ICD) implant after surgery include VT or out-of-hospital cardiac arrest, inducible VT at EPS, LV ejection fraction (LVEF) <35%, and unexplained syncope.

Baseline echocardiographic data included qualitative assessments of RV size and function and quantitative LVEF (%) on the latest evaluation before PVR (at most 3 years removed). RV dysfunction or dilatation was felt to be significant if graded to be at least moderately severe. Cardiac MRI before PVR was performed in 35 patients either in our or an outside institution.

Surgical Cryoablation
Open surgical RVOT ablation was begun in our practice in 2000 as VT treatment or prophylaxis based on preoperative conditions. During this procedure, a cryoablation lesion is placed to connect the superior aspect of the ventricular septal defect patch to the pulmonary annulus. In selected cases, a lesion grounding the ventriculotomy to the pulmonary or tricuspid annulus is performed (Figure 1). The freezes are made for 90 to 120 seconds each at −60°C with a 15-mm probe: Frigitronics (CooperVision, Inc, Lake Forest, CA) and CryoCath (Medtronic, Montreal, Quebec, Canada). Indications for surgical cryoablation of the RVOT include history of nonsustained VT or VT, inducible VT at EPS that was not ablated, and history of unexplained syncope or near syncope.

Outcome Data
The primary outcome was defined as combined event at follow-up, including VT, out-of-hospital cardiac arrest, appropriate therapy in those with ICD and SCD:

1. VT: Sustained VT documented on a 12-lead ECG, Holter recording, or ECG strips. Sustained tachycardia defined as arrhythmia lasting >30 seconds or of any length of...
time if associated with hemodynamic compromise, requiring cardioversion or admission.\textsuperscript{5,7}


3. Defibrillator discharges or antitachycardia overdrive pacing:
   - Appropriate: triggered by VT or ventricular fibrillation documented by stored intracardiac electrogram or cycle-length data in conjunction with patient’s symptoms immediately before and after device discharge.
   - Inappropriate: triggered by a rapid ventricular rate exceeding the programmed threshold rate as a consequence of supra VT, exercise-related sinus tachycardia, or a malfunction of the device.

4. SCD: Based on autopsy reports. Two patients died suddenly and were considered to succumb to SCD although no autopsy was performed.

Statistical Analysis
Descriptive statistics are reported as proportions for discrete data and mean and SDs for continuous data, except for variables that are not normally distributed in which case median and range are used. Discrete data were compared between groups using Fisher exact test. Continuous data were compared using Wilcoxon rank-sum tests. Survival and free-event times were estimated using Kaplan–Meier method with 95% confidence intervals (CIs). Survival curves were compared by the log-rank test. Cox proportional hazards models were used for the univariate analysis.

Results
A summary of the clinical characteristics is shown in Table 1. All patients had ≥1 previous operation accounting for the TOF repair and 126 of them (62%) had a transannular patch placed on the RVOT at that time. In addition, 95 patients (46%) had 2 and 35 (17%) had ≥3 previous operations including palliative surgery, closure of persistent VSD, and other residual lesions. Preoperative mean indexed RV end-systolic volume was 102±32 mL/m², RV end-diastolic volume 175±45 mL/m², and RV ejection fraction 42±8%. Their indexed LV end-systolic volume was 31±13 mL/m², LV end-diastolic volume 72±20 mL/m², and LVEF 56±8%.

Holter monitoring was abnormal for the majority of patients in whom it was available, although no VT was detected. Exercise testing before the PVR revealed nonsustained VT in 1 of the 92 patients for whom it was available; and 21 patients had repetitive VPBs in form of couplets or salvos. An EPS was conducted in 40 patients (20%) at a median time of 5 days before PVR, and pre-PVR ablation of VT was performed in 5 patients (3%). At the time of PVR, 45 patients (22%) had a QRS duration ≥180 ms, including patients with paced rhythm.

Table 1. Clinical Characteristics for Tetralogy of Fallot Patients Undergoing PVR and Comparing Patients Who Had an Event at Follow-Up and Those Who Did Not

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Yes (n=19)</th>
<th>No (n=186)</th>
<th>Total (N=205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial repair, median (IQR)</td>
<td>6.8 (4.2–12.0)</td>
<td>4.5 (2.2–7.6)</td>
<td>4.7 (2.4–8.6)</td>
</tr>
<tr>
<td>History of palliative surgery, n (%)</td>
<td>6 (32)</td>
<td>85 (46)</td>
<td>91 (44)</td>
</tr>
<tr>
<td>No. of previous interventions, median (IQR)</td>
<td>3.0 (2.0–3.0)</td>
<td>3.0 (2.0–3.0)</td>
<td>3.0 (2.0–3.0)</td>
</tr>
<tr>
<td>History of prior ventriculotomy, n (%; N=180)</td>
<td>10 (59)</td>
<td>54 (33)</td>
<td>64 (36)</td>
</tr>
<tr>
<td>History of syncope, n (%)</td>
<td>3 (16)</td>
<td>16 (9)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Lown criteria 4a or 4b, n (%; N=46)</td>
<td>3 (100)</td>
<td>28 (65)</td>
<td>31 (67)</td>
</tr>
<tr>
<td>Documented spontaneous NSVT, n (%)</td>
<td>0 (0)</td>
<td>21 (11)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>NSVT inducible at EPS, n (%; N=40)</td>
<td>1 (13)</td>
<td>3 (9)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>History of VT, n (%)</td>
<td>5 (26)</td>
<td>11 (6)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>VT inducible at EPS, n (%; N=40)</td>
<td>6 (75)</td>
<td>15 (47)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>History of ICD implantation, n (%)</td>
<td>4 (21)</td>
<td>11 (6)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Age at PVR surgery, median (IQR)</td>
<td>40.2 (26.6–55.3)</td>
<td>31.6 (19.7–45.1)</td>
<td>32.9 (20.4–46.0)</td>
</tr>
<tr>
<td>Fragmented QRS at PVR, n (%)</td>
<td>14 (82)</td>
<td>121 (69)</td>
<td>135 (66)</td>
</tr>
<tr>
<td>QRS duration at PVR, median (IQR), ms</td>
<td>170 (160–198)</td>
<td>159 (138–176)</td>
<td>160 (142–176)</td>
</tr>
<tr>
<td>LV function, median (IQR; N=189), %</td>
<td>53 (45–57)</td>
<td>57 (51–63)</td>
<td>57 (51–62)</td>
</tr>
<tr>
<td>LVEF ≤50%, n (%; N=189)</td>
<td>7 (41)</td>
<td>28 (16)</td>
<td>35 (19)</td>
</tr>
<tr>
<td>RV dysfunction, n (%; N=182)</td>
<td>5 (31)</td>
<td>19 (12)</td>
<td>24 (13)</td>
</tr>
<tr>
<td>RV dilatation, n (%; N=194)</td>
<td>13 (68)</td>
<td>107 (61)</td>
<td>120 (62)</td>
</tr>
<tr>
<td>RVOT ablation at PVR, n (%)</td>
<td>1 (5)</td>
<td>21 (11)</td>
<td>22 (11)</td>
</tr>
</tbody>
</table>

EPS indicates electrophysiological study; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LV, left ventricle; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVR, pulmonary valve replacement; RV, right ventricle; RVOT, right ventricular outflow tract; and VT, ventricular tachycardia.

*Combined event includes ventricular tachycardia, out-of-hospital cardiac arrest, appropriate therapy in those with ICD and sudden cardiac death.
Complete follow-up was available for 200 patients (98%) during a median time of 6.7 years, maximum of 24 years. The combined event occurred in 19 patients, including SCD in 5 patients, appropriate ICD therapy in 7 patients, out-of-hospital cardiac arrest in 3 patients, and clinically identified sustained VT in 4. Differences in the clinical history of this group compared with the nonevent group are detailed in Table 1. Freedom from the combined event is shown in Figure 2. Freedom from the combined event was 95.1% (95% CI, 91.8–98.5) at 5 years, 90.1% (95% CI, 84.9–95.6) at 10 years, and 79.1% (95% CI, 67.9–92.1) at 15 years. ICD placement occurred in 23 patients at a median time of 1 month after the PVR (range, 3 days to 23.5 years). A total of 7 patients had 18 appropriate discharges and 6 patients had 14 inappropriate discharges during follow-up. Two patients had only inappropriate discharges. Inappropriate discharges were because of oversensing in 43% and supraventricular tachyarrhythmia in 57%.

Univariate risk factors for the combined event are detailed in Table 2. Figure 3 shows the survival curves for freedom from any event by history of VT, LVEF, and QRS duration. Importantly, patients with LVEF <50% were >3x more likely to have RV dysfunction > moderate, hazard ratio 3.0 (95% CI, 1.4–6.8; P=0.01).

QRS duration was found to be longer in patients with an LVEF <50% (median QRS, 170 versus 158 ms; P=0.02). However, no association between QRS duration and RV function was found. All patients with prolonged QRS duration had a right bundle block pattern; therefore, no conclusion could be inferred about LV dyssynchrony and ventricular function.

QRS fragmentation was identified in 135 patients, whereas 13 patients were found to have notched QRS morphologies. Twelve patients had paced QRS morphologies and were excluded. QRS fragmentation was not predictive of the combined event. An entirely normal ECG without PR, QRS, or ST abnormality was noted in 10 patients, and none of this group sustained any event at follow-up.

Twenty-one patients died at follow-up. Three deaths occurred in the perioperative period for an operative mortality of 1.5%; cause of death was myocardial infarction, postoperative bleeding, and RV failure, respectively. Survival at 5, 10, and 15 years were 94.6% (95% CI, 91.4–97.9), 84.6% (95% CI, 78.3–91.5), and 81.7% (95% CI, 73.6–90.7), respectively.

**Surgical Cryoablation**

None of the 22 patients who underwent open surgical RVOT ablation died suddenly, sustained an out-of-hospital cardiac arrest or VT episode during follow-up. Only 1 of the 22 had an appropriate ICD discharge 7 years after surgery. In contrast, 18 of the 183 patients without surgical cryoablation sustained events: SCD (n=5), appropriate ICD therapy (n=6), out-of-hospital cardiac arrest (n=3), or VT (n=4) at follow-up. For the majority, preoperative baseline risk factors were not significantly different between these groups (Table 3), although patients in the cryoablation group were older at PVR and were more likely to have inducible VT at EPS. ICD implantation was more common in this group. Figure 4 shows the survival curve for freedom from any event by surgical cryoablation.
with increased risk. In addition, this study highlights that patients with a history of clinical VT at the time of PVR have an increased risk of ventricular arrhythmia/SCD at follow-up. This important and intuitive finding has not been reported previously in the literature. Nonsustained VT had been associated with appropriate ICD shocks in patients with TOF undergoing primary prevention ICD implantation.\textsuperscript{16} We found no association between nonsustained VT and events at follow-up in our patient group.

This investigation confirms that a prolonged QRS duration is predictive of ventricular arrhythmic events in patients with repaired TOF before PVR, yet interestingly, ECG criteria, such as QRS fragmentation or an entirely normal ECG, are not positively or negatively predictive. QRS fragmentation represents cardiac conduction delay and is thought to be a marker of fibrosis and scar within the myocardium. It is a marker of increased mortality and ventricular arrhythmia in patients with coronary disease\textsuperscript{17} and also portends a poor prognosis in those with arrhythmogenic RV dysplasia.\textsuperscript{11,18,19} It remains speculative as to why this feature is not predictive of arrhythmic events in TOF, yet this morphology is especially common, occurring in 70\% of repaired TOF patients. We hypothesized that an entirely normal ECG represents a less malignant phenotype. This seems to be the case in other forms of congenital heart disease,\textsuperscript{20} and it is interesting to note that patients in our study group with a normal ECG did not sustain any arrhythmic event.

**Surgical Cryoablation**

A central message from this study is that surgical cryoablation in the RVOT is safe and potentially reduces the risk of arrhythmic events after PVR. Importantly, surgical cryoablation does not seem to be proarrhythmic. A major concern with any ablation procedure (done percutaneously or via an open approach) centers on whether bidirectional block can be achieved across a corridor of electric conduction. If lesion depth is not transmural, damaged myocardium can serve as substrate providing slow cardiac conduction and thereby providing one of the key ingredients for reentrant arrhythmia. Intraoperative open EPS mapping is typically no longer performed, and therefore lesion depth/discrete linear block cannot be confirmed during open cryoablation cases. Although underpowered because of small numbers and low event rates, these data do suggest a trend toward surgical cryoablation of the RVOT being associated with less post-PVR ventricular arrhythmic events. Only 1 patient sustained an appropriate ICD discharge 7 years after the PVR/cryoablation procedure. This is especially important information given that the literature is currently limited to only 9 patients from a small series and follow-up limited to 5 years.\textsuperscript{5}
Electrophysiological Studies

A remaining question therefore in managing the risk of serious ventricular arrhythmia in TOF patients with pulmonary regurgitation revolves around the need for an EPS and its optimal timing. The highest risk group in the study is TOF/PVR patients with prior documentation of VT; we suggest these patients undergo preoperative EPS to more carefully assess risk of malignant events. It is a concern, however, that ventricular arrhythmia before PVR is in part related to the volume overloading RV, and improvement in the hemodynamic milieu with PVR offloads the RV, reduces myocardial stretch, and thereby allows for geometric and electric remodeling. A significant reduction in the incidence of monomorphic VT after PVR has been previously recognized.\(^5,21\) In these analyses, appropriate ICD therapy was not included as an endpoint. Although data from this current study does reflect a similar trend, with the prevalence of VT decreasing after PVR, patients with history of VT have a higher risk of ventricular arrhythmia/SCD at follow-up. The majority of events occurred in patients who did not undergo pre- or postoperative EPS. These findings suggest that all patients with risk factors for VT undergoing PVR should have an EPS pre- or postoperatively. Additional study is required to determine whether this study can potentially be applied to all patients in this report underwent PVR which can improve arrhythmogenic substrate.

Patients with syncope do seem to be a high-risk group with the vast majority in this cohort undergoing EPS, surgical cryoablation, or ICD implantation.

Limitations

The retrospective historical nature of the study is inherently limited, but given the small population with congenital heart disease, this is unfortunately integral to current investigation in this setting. Recommendations for monitoring patients with pulmonary valve regurgitation after TOF repair and determining optimal timing of PVR changed during the course of the study period and thus testing and referral patterns varied during the study. Although preoperative Holter monitoring was available for a limited number of patients, we considered worth including in the analysis as there are few publications with that many patients. However, qualitative RV dimensions and function were measured by echocardiography given the small number of MRIs performed preoperatively. Although the surgical cryoablation analysis is underpowered because of small numbers and low event rates, to our knowledge represents the larger number of patients ever studied.

Conclusions

Patients with repaired TOF undergoing PVR with a history of VT, QRS ≥180 ms, and LVEF <50% are at high risk of arrhythmic events after operation. Our findings suggest that an EPS should be strongly considered in this particularly high-risk group before or after PVR. Surgical cryoablation at the time of PVR does not seem to be proarrhythmic and may be beneficial.

We recommend a comprehensive multidisciplinary preoperative evaluation for all TOF patients with pulmonary valve regurgitation to determine the best timing of operation and the extent of preoperative VT risk stratification. Based on these data we suggest that the preoperative VT risk assessment include ECG, Holter, exercise testing, and EPS for patients with high-risk features. We currently advise that TOF patients undergoing PVR who have preoperative syncope, VT, or abnormal EPS undergo surgical cryoablation or ICD implantation.

Future initiatives in this field should include multicenter collaborative studies to validate these findings.

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Disclosures

None.

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