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ORIGINAL ARTICLE

# Systematic Electrophysiological Study Prior to Pulmonary Valve Replacement in Tetralogy of Fallot: A Prospective Multicenter Study

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**BACKGROUND:** Ventricular arrhythmias and sudden death are recognized complications in tetralogy of Fallot. Electrophysiological studies (EPS) before pulmonary valve replacement (PVR), the most common reintervention in tetralogy of Fallot, could potentially inform therapy to improve arrhythmic outcomes.

**METHODS:** A prospective multicenter study was conducted to systematically assess EPS with programmed ventricular stimulation in patients with tetralogy of Fallot referred for PVR from January 2020 to December 2021. A standardized stimulation protocol was used across all centers.

**RESULTS:** A total of 120 patients were enrolled, mean age 39.2±14.5 years, 53.3% males. Sustained ventricular tachycardia was induced in 27 (22.5%) patients. When identifiable, the critical isthmus most commonly implicated (ie, in 90.0%) was between the ventricular septal defect patch and pulmonary annulus. Factors independently associated with inducible ventricular tachycardia were history of atrial arrhythmia (odds ratio, 8.56 [95% CI, 2.43–34.73]) and pulmonary annulus diameter >26 mm (odds ratio, 5.05 [95% CI, 1.47–21.69]). The EPS led to a substantial change in management in 23 (19.2%) cases: 18 (15.0%) had catheter ablation, 3 (2.5%) surgical cryoablation during PVR, and 9 (7.5%) defibrillator implantation. Repeat EPS 5.1 (4.8–6.2) months after PVR was negative in 8 of 9 (88.9%) patients. No patient experienced a sustained ventricular arrhythmia during 13 (6.1–20.1) months of follow-up.

**CONCLUSIONS:** Systematically performing programmed ventricular stimulation in patients with tetralogy of Fallot referred for PVR yields a high rate of inducible ventricular tachycardia and carries the potential to alter management. It remains to be determined whether a standardized treatment approach based on the results of EPS will translate into improved outcomes.

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**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** electrophysiological study ■ implantable cardioverter defibrillator ■ pulmonary valve replacement ■ sudden death ■ tetralogy of Fallot ■ ventricular arrhythmia

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### WHAT IS KNOWN?

- Ventricular arrhythmias and sudden death are recognized complications in tetralogy of Fallot (TOF).
- Pulmonary valve replacement (PVR) is the most common reintervention in this population.

### WHAT THE STUDY ADDS

- Systematically performing electrophysiological studies in patients with TOF referred for PVR yields a high rate of inducible ventricular tachycardia and carries the potential to alter management.
- Further research is needed to assess the potential role of prophylactic catheter ablation in patients without inducible ventricular arrhythmia in this setting.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **EPS** | electrophysiological study |
| **ICD** | implantable cardioverter defibrillator |
| **IQR** | interquartile range |
| **PVR** | pulmonary valve replacement |
| **PVS** | programmed ventricular stimulation |
| **RV** | right ventricle |
| **SCD** | sudden cardiac death |
| **TOF** | tetralogy of Fallot |
| **VA** | ventricular arrhythmia |
| **VF** | ventricular fibrillation |
| **VSD** | ventricular septal defect |
| **VT** | ventricular tachycardia |

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect.[1] Although long-term survival after repair is excellent,[2] surgical scarring exposes patients to the occurrence of ventricular arrhythmias (VAs) and sudden cardiac death (SCD) that remain important issues in this population.[3–7]

During surgical repair, the integrity of the pulmonary valve is often disrupted to effectively relieve the obstructed right ventricular outflow tract, which results in a high degree of pulmonary regurgitation in most patients. Pulmonary valve replacement (PVR) is, therefore, the most common reintervention in this population with an annual rate of 0.8%,[8] whether it be surgical or percutaneous.[9] Electrophysiological studies (EPS) are commonly used to risk stratify patients with TOF and have been proposed as means of systematically assessing risk for VAs before PVR in different expert centers. The rationale for such an approach is that patients with TOF who require PVR have a constellation of factors that renders them at higher risk for VAs,[10] and that the pulmonary prosthesis may cover parts of the infundibular septum and interfere with later attempts to transect the isthmus by ablation.[11] Moreover, transmural surgical ablation lines can be performed if a critical isthmus is identified during preoperative mapping by applying both endocardial and epicardial lesions. However, no large-scale study has yet prospectively assessed programmed ventricular stimulation (PVS) studies before PVR in patients with TOF. Consequently, international guidelines concede that the relevance of systematically performing PVS in patients without documented VAs remains unknown.[12]

A prospective multicenter study was conducted to systematically assess the yield of EPS with PVS in patients with TOF referred for PVR using a standardized stimulation, and assess associated factors.

## METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure upon reasonable request.

### Study Setting and Population

This prospective multicenter study included all consecutives patients with TOF referred for PVR, either surgically or percutaneously, in 5 tertiary centers in France: European Georges Pompidou, Paris; Louis Pradel Hospital, Lyon; Marie-Lannelongue Hospital, Le Plessis-Robinson; Necker Hospital, Paris; and Pasteur Clinic, Toulouse. These hospitals are national referral centers for congenital heart diseases and include multidisciplinary teams with cardiologists, interventional cardiologists, surgeons, imaging specialists, anesthesiologists, and electrophysiologists specifically trained in congenital heart diseases. Patients were enrolled during a 2-year period spanning from January 1, 2020 to December 31, 2021 (NCT04205461). Patients with unrepaired TOF and those who refused a pre-PVR EPS were excluded.

This study was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté) and approved by the appropriate institutional review boards. Data were centralized, collected and managed using REDCap electronic data capture tools hosted at the Paris Cardiovascular Research Center (Inserm 970, European Georges Pompidou Hospital, Paris, France). Written informed consent was obtained in all patients.

### Electrophysiological Study

A common predefined protocol was used across the different centers. A preprocedural cardiac computed tomography-scan was systematically performed to rule-out thrombus, to analyze the underlying anatomy, and for 3D-image integration. All antiarrhythmic drugs were interrupted for at least 5 half-lives before the procedure. The EPS was performed under local anesthesia or deep sedation, except in patients with intellectual disabilities or major anxieties that rendered general anesthesia the preferred approach. Programmed right ventricle (RV) stimulation was performed at 2 sites (ie, apex and outflow tract), at 2 cycle lengths (ie, 600 and 400 milliseconds), and using up to 3 additional extrastimuli until the RV refractory period

or 170 milliseconds. If the study was negative, the protocol was repeated after an isoproterenol infusion with the objective to accelerate the sinus rhythm to >130 bpm. If a positive PVS study was followed by catheter ablation, electroanatomical mapping with the CARTO system (Biosense Webster) was used. High-density RV voltage (including late potentials and local abnormal ventricular activities) and activation maps were performed in sinus rhythm and during ventricular tachycardia (VT) to identify critical slowly conducting anatomical isthmuses. Pace mapping approach was also used in patients with unstable VT. Irrigated radiofrequency was used for catheter ablation (40–50 Watts, Smartouch catheter, Biosense Webster). Acute ablation success was defined as noninducibility and demonstration of bidirectional block across ablation lines by pacing maneuvers and activation maps. Prophylactic catheter ablation was performed in selected patients with negative PVS but with either a high burden of premature ventricular complexes or documented clinical nonsustained VT or with nonsustained VAs induced during PVS. In those patients, potential critical isthmuses were identified after electroanatomical mapping and conduction velocity analysis. A slow conducting isthmus was defined as having a conduction velocity in sinus rhythm <0.5 m/s.[10] Electroanatomical mapping was not systematically performed in patients without inducible VT who did not undergo catheter ablation.

### Collected Data

Baseline information before EPS was collected on demographic characteristics, medical history, and details of TOF including date and types of previous cardiac surgeries. History of supraventricular and VAs, catheter ablation procedures, congestive heart failure, cardiovascular symptoms, and pharmacological treatment were also recorded. Findings from 12-lead electrocardiograms, 24-hour Holter monitors, and cardiac imaging (echocardiography and cardiac magnetic resonance imaging) were also analyzed. Previously reported definitions were used for QRS fragmentation criteria with observers blinded to patient characteristics and outcomes.[13] Electronic calipers were used for electrocardiogram measurements (Compas EP software, EP studio). The most recent data preceding EPS were selected, with a maximum acceptable time interval of 1 year.

### Outcomes

The primary outcome was a positive PVS, defined as inducibility of a sustained VA (ie, >30 seconds). Inducible VAs were classified as monomorphic VT or polymorphic VT/ventricular fibrillation (VF). As a secondary exploratory outcome, the proportion of patients was assessed in whom the EPS before PVR resulted in a major change in management as defined by catheter or surgical VT ablation or insertion of an implantable cardioverter defibrillator (ICD). Arrhythmic events during the prospective follow-up after EPS and after PVR were also recorded.

### Statistical Analysis

This report was prepared in compliance with the STROBE checklist (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies.[14] Categorical data were reported as numbers and percentages. Continuous data were summarized as mean±SD or median and interquartile range (IQR) for normally and nonnormally distributed data, respectively. Comparisons were performed using the $\chi^2$ or Fisher exact test for categorical variables and Student *t* test or Mann–Whitney–Wilcoxon test, when appropriate, for continuous variables. Logistic regression models were used to identify factors associated with a positive PVS. Variables with *P*-values <0.1 in univariable analyses were considered in multivariable models, with the final model selection based on the most favorable goodness-of-fit measures (Bayesian information criterion). The risk score reported by Khairy and colleagues was also calculated in all patients, but the left ventricular end-diastolic pressure was not integrated because not systematically measured during EPS in our protocol.[15] Two-tailed *P*-values <0.05 were considered statistically significant. All data were analyzed at INSERM, Unit 970, Cardiovascular Epidemiology and Sudden Death, Paris, using the *R* software, version 3.6.3 (R Project for Statistical Computing, Vienna, Austria).

## RESULTS

### Patients' Characteristics

A total of 120 patients were enrolled, mean age 39.2±14.5 years, 53.3% males, during a 2-year period. The main clinical characteristics of patients at the time of EPS are presented in Table 1. Characteristics of patients who did not undergo EPS before PVR during the same period of time are presented in Table S1. The median (IQR) age at corrective surgery was 3.9 (0.7–8.2) years with a mean delay from surgery to EPS of 33.6±10.9 years. Fifteen patients had a prior PVR and were referred for a second intervention. A syndromic context was present in 13 (10.8%) patients, with DiGeorge syndrome in 7. Before the EPS, 4 (3.3%) patients had received an ICD, including 2 [50.0%] for secondary prevention. Two (1.7%) patients had a previous catheter ablation procedure for a VA. Thirty (25.0%) patients were on B-blockers, 6 (5.0%) on amiodarone, 2 (1.7%) on sotalol, and 1 (0.8%) on flecainide.

### Electrophysiological Study

The EPS was performed under local anesthesia in 93 (77.5%) patients, deep sedation in 12 (10.0%), and general anesthesia in 15 (12.5%). The PVS was positive in 27 (22.5%) patients. At least 1 monomorphic VT was induced in 22 (18.3%) patients and at least 1 polymorphic VT/VF was induced in 8 (6.7%) patients, with 3 patients having both inducible monomorphic VT and polymorphic VT/VF. Characteristics of patients with monomorphic versus polymorphic VT/VF are presented in Table S2. The median (IQR) VT cycle length for induced monomorphic VTs was 240 (200–270) milliseconds. Two patients with monomorphic VT had 2 different VTs induced. Among those with ICDs pre-EPS, the PVS was negative in both patients with secondary

**Table 1. Characteristics of Patients at the Time of Electrophysiological Study**

| | All patients N=120 | Positive PVS n=27 | Negative PVS n=93 | *P* |
|---|---|---|---|---|
| Age, y; mean±SD | 39.2±14.5 | 46.9±13.8 | 37.0±14.1 | 0.002 |
| Male, n (%) | 64 (53.3) | 16 (59.3) | 48 (51.6) | 0.630 |
| Prior palliative shunt, n (%) | 45 (38.8) | 16 (59.3) | 29 (32.6) | 0.023 |
| Delay from corrective surgery, y; mean±SD | 33.6±10.9 | 39.9±10.3 | 31.7±10.4 | 0.001 |
| Ventriculotomy incision, n (%) | 78 (88.6) | 20 (95.2) | 58 (86.6) | 0.440 |
| Transannular patch, n (%) | 63 (80.8) | 17 (89.5) | 46 (78.0) | 0.336 |
| Number of prior cardiac surgery, median (IQR) | 1 (1–2) | 2 (1–2) | 1 (1–2) | 0.084 |
| Previous PVR, n (%) | 15 (12.5) | 3 (11.1) | 12 (12.9) | 1 |
| History of syncope, n (%) | 2 (1.7) | 1 (3.7) | 1 (1.1) | 0.401 |
| History of congestive heart failure, n (%) | 11 (9.2) | 5 (18.5) | 6 (6.5) | 0.121 |
| History of atrial arrhythmia, n (%) | 31 (25.8) | 17 (63.0) | 14 (15.1) | <0.001 |
| History of nonsustained VT, n (%) | 10 (8.3) | 2 (7.4) | 8 (8.6) | 1 |
| History of sustained VT/VF, n (%) | 4 (3.3) | 1 (3.7) | 3 (3.2) | 1 |
| History of palpitations, n (%) | 34 (28.3) | 8 (29.6) | 26 (28.0) | 1 |
| NYHA class, n (%) | | | | 0.010 |
| I | 43 (37.7) | 7 (26.9) | 36 (40.9) | |
| II | 54 (47.4) | 10 (38.5) | 44 (50.0) | |
| III | 17 (14.9) | 9 (34.6) | 8 (9.1) | |
| QRS duration, ms; mean±SD | 151±31 | 162±34 | 149±31 | 0.229 |
| QRS duration ≥180 ms; n (%) | 16 (18.0) | 3 (21.4) | 13 (17.3) | 0.711 |
| QRS fragmentation, n (%) | 43 (35.8) | 12 (44.4) | 31 (33.3) | 0.405 |
| Left ventricular ejection fraction (%); mean±SD | 59±8 | 61±9 | 59±8 | 0.188 |
| Right ventricular ejection fraction (%); mean±SD | 43±9 | 40±7 | 44±9 | 0.036 |
| Indexed RV end-diastolic diameter, mm/m$^2$; mean ±SD | 158±39 | 164±49 | 156±35 | 0.448 |
| Pulmonary annulus diameter, mm; mean±SD | 28.1±7.3 | 32.0±7.1 | 26.8±6.9 | 0.004 |

IQR indicates interquartile range; LVEDP, left ventricular end-diastolic pressure; NYHA, New York Heart Association; PVR, pulmonary valve replacement; PVS, programmed ventricular stimulation; RV, right ventricle; VF, ventricular fibrillation; and VT, ventricular tachycardia.

prevention indications and positive in 1 (50.0%) patient with a primary prevention ICD. Overall, 1 (0.8%) patient had a complication related to the EPS, which consisted of a femoral pseudoaneurysm that did not require interventional management.

## VT Ablation

After PVS, catheter ablation was performed in 24 (20.0%) patients, including 18 (75.0%) with positive PVS and 6 (25.0%) with a negative PVS (prophylactic ablation; Figure 1). When the critical isthmus could be identified (n=20), the isthmus between the ventricular septal defect (VSD) patch and the pulmonary artery valve (ie, isthmus 3) was involved in 18 (90.0%), the isthmus between the tricuspid annulus and the ventriculotomy scar (ie, isthmus 1) in 2 (10.0%), the isthmus between the ventriculotomy scar and the pulmonary valve in 1 (5.0%; ie, isthmus 2), and the isthmus between the VSD patch and the tricuspid annulus in 1 (5.0%; ie, isthmus 4). At the end of the procedure, 15 (83.3%) patients had no more inducible VA, whereas 2 (8.3%) still had inducible polymorphic VT/VF and 1 (4.2%) had persistently inducible monomorphic VT. Except for the latter patient that remained inducible with failure to achieve bidirectional block across isthmus 3, conduction block was validated in all other targeted isthmuses. The patient with persistent monomorphic VT and failed catheter ablation had surgical cryoablation of isthmus 3 during PVR. Two additional patients with inducible VT involving isthmus 3 had surgical ablation at the time of PVR without a prior attempt at catheter ablation.

No catheter or surgical ablation was performed in 7 patients despite a positive PVS: 5 had inducible polymorphic VT/VF and the 2 other patients had fast poorly tolerated monomorphic VT not related to isthmus 3 and underwent ICD implantations.

## Factors Associated With Positive PVS

Patient characteristics associated with a positive PVS are presented in Table 2. In multivariable analysis, history of atrial arrhythmia (odds ratio, 8.56 [95% CI, 2.43–34.73]; *P*=0.001) and pulmonary annulus diameter >26 mm (odds ratio, 5.05 [95% CI, 1.47–21.69]; *P*=0.016) remained independently associated with a positive PVS. Nonsustained VT (*P*=1.0), left ventricular ejection fraction (*P*=0.95), QRS duration ≥180 milliseconds (*P*=0.71), and QRS fragmentation (*P*=0.41) were not associated with a positive PVS. There were no statistically significant differences in the proportion of inducible patients under local anesthesia/deep sedation (25/105, 23.8%) versus general anesthesia (2/15, 13.3%; *P*=0.52) or with pulmonary valve regurgitation (20/87, 23.0%) versus stenosis (7/33, 21.2%; *P*=0.94). The Khairy's risk score of patients is presented in Table 3 according to the result of the PVS.

## Impact of EPS on Patient Management

The impact of EPS on ablation and ICD implantation is summarized in Figure 1. Among the 27 (22.5%) patients

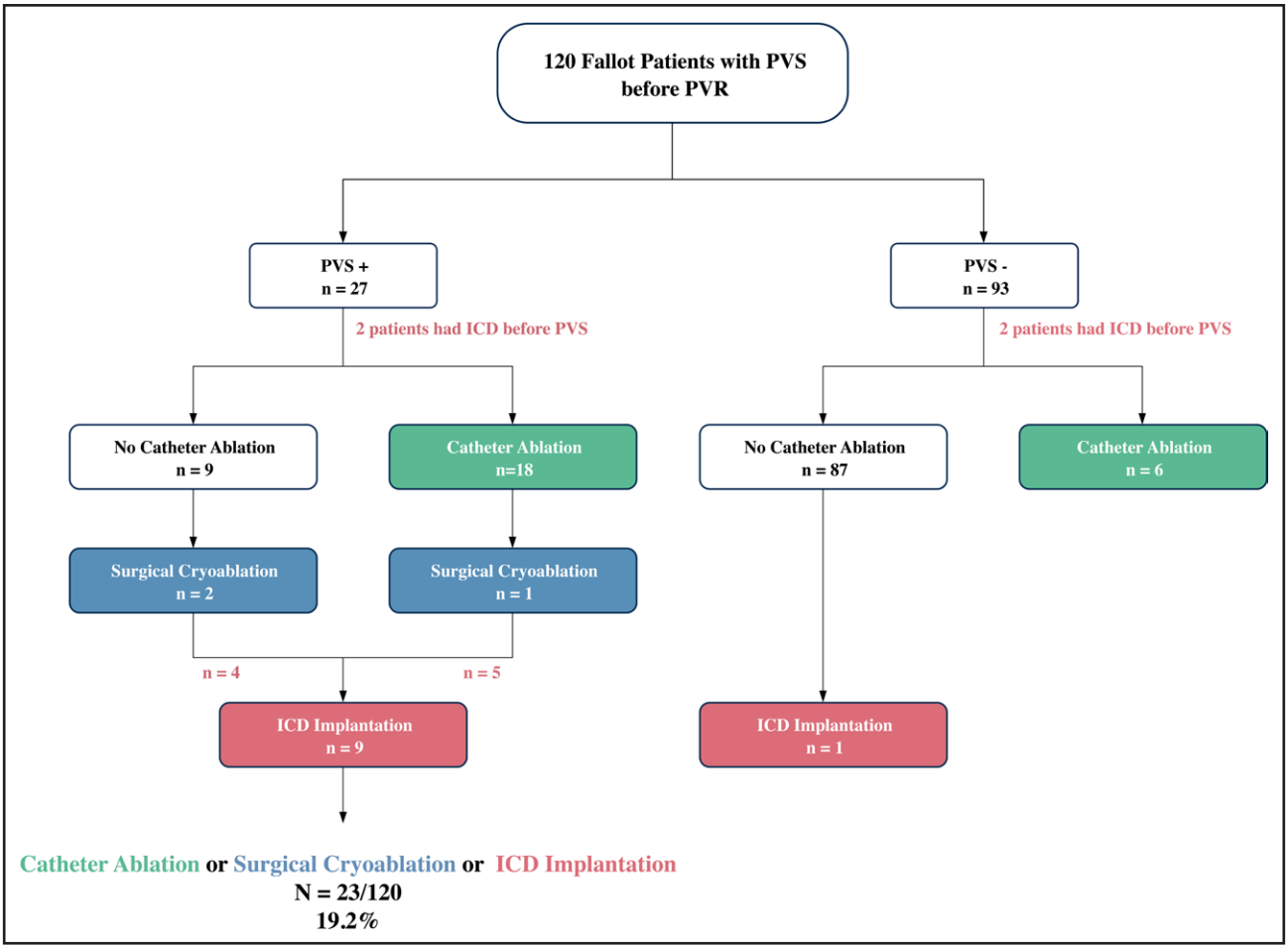


**Figure 1. Impact of electrophysiological study on patients' management.**

with a positive PVS, 18 (66.7%) had catheter ablation, 3 (11.1%) had surgical cryoablation, and 9 (33.3%) had ICD implantation. Overall, the EPS resulted in a change in patient management in 23 (19.2%) patients.

Among the 93 (77.5%) patients with a negative PVS, 6 (6.5%) had prophylactic catheter ablation, and 1 (1.1%) had ICD implantation for severe left ventricular dysfunction associated with a QRS >180 milliseconds

**Table 2. Factors Associated With a Positive Programmed Ventricular Stimulation**

| | Positive PVS (n=27) | Negative PVS (n=93) | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | *P* | OR (95% CI) | ***b*** |
| Age, y; mean±SD | 46.9±13.8 | 37.0±14.1 | 1.05 (1.02–1.09)* | 0.002 | 1.01 (0.96–1.06)* | 0.716 |
| Delay from corrective surgery, y; mean±SD | 39.9±10.3 | 31.7±10.4 | 1.08 (1.03–1.13)* | 0.001 | – | |
| Corrective surgery before 1990, n (%) | 22 (81.5) | 46 (50.0) | 4.26 (1.57–13.9) | 0.007 | – | |
| Prior palliative shunt, n (%) | 16 (59.3) | 29 (32.6) | 2.97 (1.23–7.44) | 0.023 | – | |
| History of atrial arrhythmia, n (%) | 17 (63.0) | 14 (15.1) | 9.28 (3.59–25.5) | <0.001 | 8.56 (2.43–34.73) | 0.001 |
| NYHA class ≥III; n (%) | 9 (34.6) | 8 (9.1) | 5.18 (1.72–16.0) | 0.003 | – | |
| Right ventricular ejection fraction (%); mean±SD | 40±7 | 44±9 | 0.94 (0.89–0.99)† | 0.036 | – | |
| Pulmonary annulus diameter, mm; mean ±SD | 32.0±7.1 | 26.8±6.9 | 1.11 (1.03–1.20)‡ | 0.004 | – | |
| Pulmonary annulus diameter >26 mm; n (%) | 19 (82.6) | 34 (50.0) | 4.56 (1.51–17.5) | 0.013 | 5.05 (1.47–21.69) | 0.016 |

NYHA, indicates New York Heart Association; OR, odds ratio; PVS, programmed ventricular stimulation.
*Per year increment.
†Per 1% increment.
‡Per 1 mm increment.

**Table 3. Khairy's Risk Score According to PVS Result**

| Khairy's risk score (without LVEDP*) | Positive PVS (n=27) | Negative PVS (n=93) | *P* |
|---|---|---|---|
| Considering PVS result† | | | |
| Median (IQR) | 4 (4–6) | 2 (0–2) | <0.001 |
| Low risk (0–2); n (%) | 5 (6.1) | 77 (93.9) | |
| Intermediate risk (3–5); n (%) | 11 (42.3) | 15 (57.7) | |
| High risk (6–12); n (%) | 11 (91.7) | 1 (8.3) | |
| Without considering PVS result† | | | |
| Median (IQR) | 2 (2–4) | 2 (0–2) | 0.009 |
| Low risk (0–2); n (%) | 15 (16.3) | 77 (83.7) | |
| Intermediate risk (3–5); n (%) | 12 (44.4) | 15 (55.6) | |
| High risk (6–12); n (%) | 0 (0.0) | 1 (100.0) | |

EPS indicates electrophysiological study; IQR, interquartile range; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary valve replacement; and PVS, programmed ventricular stimulation.

*LVEDP (accounting for 3/12 points in the score) was not integrated because not systematically measured during EPS in our protocol.

†To assess in which extent this risk score may predict the PVS result before PVR, the risk score is provided considering or not the PVS result because inducible ventricular tachycardia is part of the risk score.

and a significant burden of premature ventricular complexes. If these patients were considered, the EPS resulted in a change in patient management in 30 (25.0%) patients.

## Events During Follow-Up

The median (IQR) follow-up duration after EPS study was 13 (6.1–20.1) months. A total of 106 (88.3%) patients had PVR after a median (IQR) of 3.0 (1.0–6.2) months, including 45 (42.3%) percutaneously and 61 (57.7%) surgically (including 4 after percutaneous PVR failure). The remaining 14 (11.7%) patients are awaiting PVR. No patient experienced a sustained VA or appropriate ICD therapy during follow-up. Two (1.7%) patients died (1 from perioperative stroke and 1 from septic shock) and 1 (0.8%) patient underwent heart transplantation.

A repeat PVS was performed in the absence of a documented or suspected clinical VA in 11 patients with an initially positive PVS a median (IQR) of 8.7 (6.3–11.1) months after the initial procedure. In 9 patients, it was performed post PVR and in 2 before PVR. The median (IQR) delay between PVR and repeat PVS was 5.1 (4.8–6.2) months. The repeat PVS was negative in 8 of 9 (88.9%) patients post PVR and in 1 of 2 (50.0%) patients before PVR. The patient that remained inducible post PVR had ICD implantation without catheter ablation in the context of rapid poorly tolerated VT (cycle length 200 milliseconds) in proximity to the prothesis. The patient with inducible VT on repeat PVS before PVR had recovered conduction across isthmus 3 and underwent redo ablation with bidirectional block and noninducibility achieved before the surgical intervention. The results of the repeat PVSs are summarized in Figure 2.

# DISCUSSION

This multicenter study is the largest prospective assessment of PVS before PVR in patients with TOF and, to our knowledge, the first to use a predefined uniform PVS protocol across all centers. Key findings are as follows: (1) systematically performing EPS before PVR in patients with TOF identifies a substantial proportion of patients with inducible VAs; (2) factors independently associated with inducible VAs in this targeted population of patients with TOF were prior atrial arrhythmias and a pulmonary annulus diameter >26 mm; (3) systematically performing EPS before PVR had major implications on catheter or surgical VT ablation and ICD implantation; and (4) the majority of patients with repeat EPS who had inducible VAs before PVR were noninducible post PVR.

The rationale to perform EPS before PVR in patients with TOF encompasses both the known increased risk for VAs associated with unfavorable hemodynamics and the fact that the pulmonary prosthesis may cover parts of the infundibular septum and prevent subsequent attempts to transect the isthmus by ablation.[11] The substrate for VAs in patients with repaired TOF mainly involve well-defined anatomical isthmuses between the VSD patch, pulmonary valve, right ventricular incision, and tricuspid annulus. Isthmus 3 between the VSD patch and pulmonary valve is the most commonly implicated isthmus[10,16–19] and the one most likely to be rendered incompletely accessible post PVR. Moreover, EPS before PVR can guide concomitant surgical cryoablation if a critical isthmus is identified during preoperative mapping and catheter ablation is either not performed or unsuccessful in achieving bidirectional block and noninducibility. Furthermore, there is some evidence to suggest that catheter ablation is preferable before PVR in order to avoid mechanical trauma and potential infectious complications (endocarditis) associated with ablation after valve insertion.[20]

International guidelines now recommend electrophysiologic evaluation before PVR in patients with a history of sustained VT.[12] The impact of systematic preinterventional mapping and preventive ablation in patients without documented sustained VAs remains uncertain. Sandhu and colleagues reported their experience in 70 patients with TOF who underwent a pre-PVR EPS in 2 centers.[21] In their cohort, 34 (49%) patients were inducible, no VT mapping was performed, and most inducible patients underwent empirical surgical cryoablation during PVR. Among patients with surgical cryoablation (n=31), 14 (47%) remained inducible after PVR and subsequently underwent ICD implantation. In our study, the proportion with positive PVS was substantial but lower (23%), likely due in part to a less selected population given that EPS

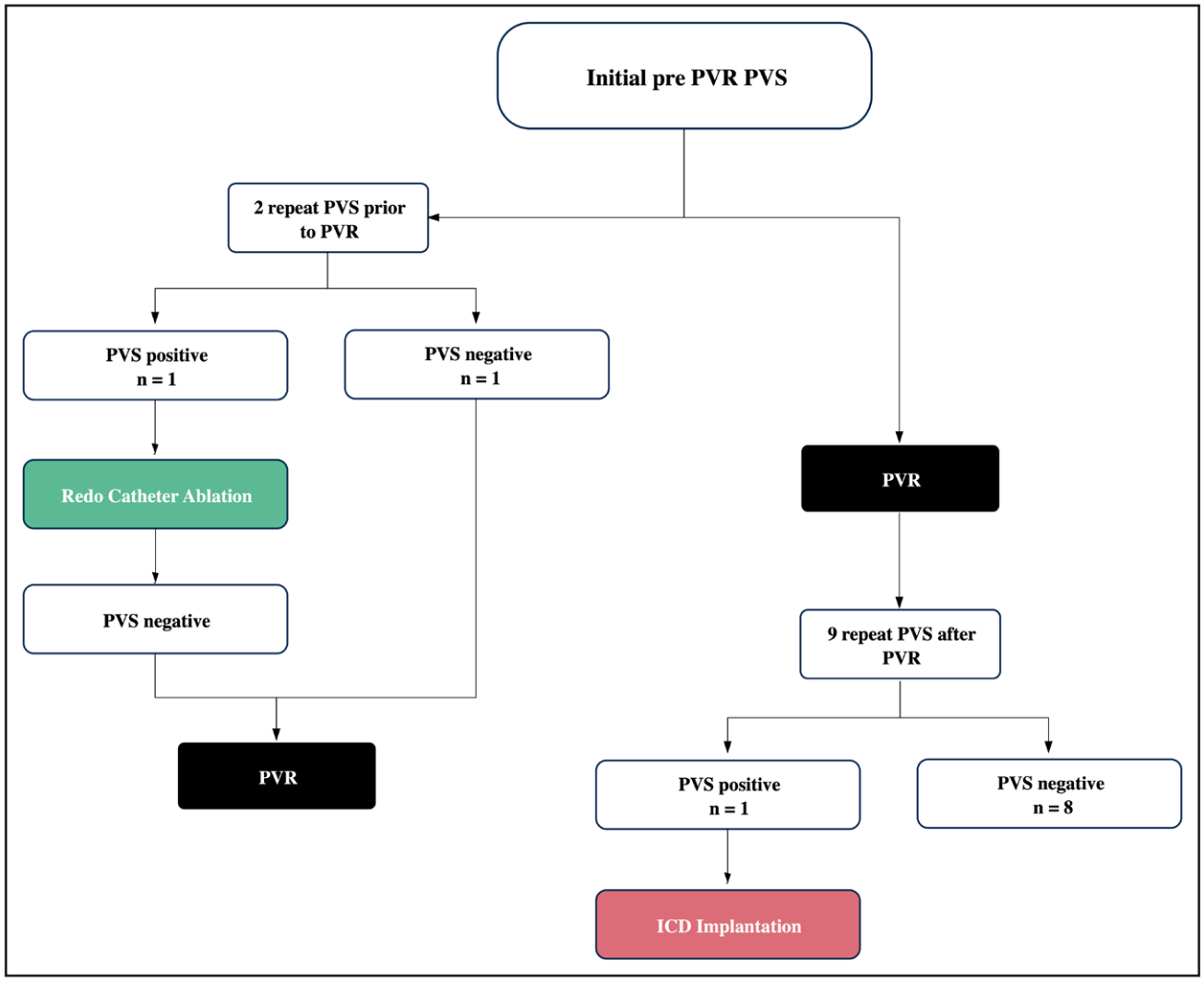


**Figure 2. Results of repeat programmed ventricular stimulations.**

was systematically performed in almost all patients with TOF before PVR.

In addition to catheter ablation in most inducible patients, a few had surgical cryoablation as a first-line approach or after failure of catheter ablation. A few other patients with negative PVS also underwent substrate-based catheter ablation, with potential critical isthmuses identified using electroanatomical mapping and conduction velocity analysis.[10] Although the present study was not designed to assess a protocol-defined management scheme based on the results of PVS, the approach had important clinical implications that altered management in 19% of patients. Furthermore, although a repeated PVS after PVR was not systematically performed in all patients, unlike the study by Sandhu et al, only 11% remained inducible post PVR after substrate ablation. We can hypothesize that our targeted approach of ablating identified potential critical isthmuses for VT yields superior outcomes to an empiric ablation approach based on VT inducibility alone.

Different clinical parameters associated with a positive PVS in the population of patients with TOF before PVR were identified. The multivariable association between history of atrial arrhythmias and inducible VAs likely reflects shared cofactors as opposed to a causal link. Importantly, our study found an independent association between a larger pulmonary annulus and a positive PVS. Indeed, increased ventricular volumes have been associated with lower ventricular effective refractory periods, slower conduction, and increased dispersion of refractoriness that could predispose to arrhythmias.[22] The RV volume was not statistically associated with inducibility in our study, possibly due to the size of our sample, and because most of the circuits in TOF turn around the right ventricular outflow tract involving a critical anatomical isthmus between the pulmonary valve and the VSD patch, the pulmonary annulus diameter may be a better predictor of VAs and positive PVS rather than RV volume in these patients. The association between pulmonary annular dimension and risk for VA/SCD in patients with

TOF merits further study. Arrhythmic risk does appear to be impacted by right ventricular remodeling resulting from chronic pulmonary regurgitation. While optimal indications and timing for PVR remain uncertain in asymptomatic patients, it remains to be determined whether earlier interventions based on the pulmonary annular size may be associated with a lower risk of subsequent VAs.[23] It may also be prudent to avoid large ventriculotomies that transect the pulmonary annulus and increase the diameter of the right ventricular outflow tract during the initial repair to reduce the long-term risk for VAs.

The systematic approach to EPS before PVR was associated with a very low rate of complications (ie, only 1 minor vascular complication in our cohort). Beyond detailed studies performed in those with inducible VT, it remains to be determined whether analyzing all potential critical isthmuses for VT, even in those who are noninducible, could favorably impact outcomes. In particular, potential critical isthmuses with slow conduction velocities (<0.5 m/s) have been associated with risk for VAs.[10] The clinical impact of substrate-based ablation in patients with slow conducting isthmuses but negative PVS remains uncertain. If evidence progressively emerges, a future challenge will be to determine whether patients with slowly conducting isthmuses could be identified noninvasively, such as by combining clinical and imaging data with computational analyses.[24] Furthermore, approaches during corrective surgery for TOF that limit the number of potential critical isthmuses for VT (eg, transatrial-transpulmonary approach) should be favored whenever feasible because they may reduce future risks of developing VAs.[25]

## Limitations

The study is the largest systematic appraisal of EPS before PVR in patients with TOF. However, there was no protocol-defined requirement to systematically perform post PVR. Such an approach could have provided more robust estimates of post PVR inducibility rates, along with interesting additional information on the durability of ablation lesions performed before or at concomitant with PVR. Second, the primary outcome was inducibility during PVS before PVR. The study was not designed to assess a management strategy based on the results of EPS or on VA/SCD outcomes post PVR. Follow-up after the EPS was limited to a median of 13 months. In comparison, the mean time to first appropriate ICD shock was 3.6 years in the study by Sandhu et al. Moreover, in the largest study evaluating the value of PVS in TOF (not specifically in the PVR context), the cumulative incidence of VT or SCD was 17.3% and 20.8% at 5 and 10 years, respectively.[26] A direct comparison of this approach (systematic PVS before PVR) with a control group would be highly informative but would require a very large population, long-term follow-up, and preferably a randomized design with a standardized protocol-defined management scheme based on the PVS result to assess the impact of this strategy on hard outcomes. Finally, magnetic resonance imaging was not standardized, and there were no uniform criteria for late gadolinium enhancement across the different centers. Hence, we were unable to assess correlation between inducibility and the amount and location of fibrosis, which is increasingly recognized as a valuable risk marker.

## Conclusions

In this large prospective multicenter study, systematically performing EPS in patients with TOF referred for PVR yielded a high rate of inducible VAs. This approach, therefore, carries the potential to substantially impact patient management peri-PVR. It remains to be determined whether a standardized treatment approach based on the results of a pre-PVR EPS will result in lower incidence of VAs and SCD in patients with TOF.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Tables S1–S2

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