Received: 3 February 2023 | Revised: 27 April 2023 | Accepted: 12 May 2023

DOI: 10.1111/jce.15940

ORIGINAL ARTICLES

WILEY

Electrophysiological study prior to planned pulmonary valve replacement in patients with repaired tetralogy of Fallot

Benjamin Bouyer MD[1,2] | Zakaria Jalal MD, PhD[2,3] | F. Daniel Ramirez MD[4] | Nicolas Derval MD[1,2] | Xavier Iriart MD[2,3] | Josselin Duchateau MD, PhD[1,2] | François Roubertie MD, PhD[2,3] | Nadir Tafer MD[2,3] | Romain Tixier MD[1,2] | Thomas Pambrun MD[1,2] | Ghassen Cheniti MD[1,2] | Ciro Ascione MD[1,2] | Masaaki Yokoyama MD[1,2] | Christopher Kowalewski MD[1,2] | Samuel Buliard MD[1,2] | Rémi Chauvel MD[1,2] | Marine Arnaud MD[1,2] | Mélèze Hocini MD[1,2] | Michel Haïssaguerre MD[1,2] | Pierre Jaïs MD, PhD[1,2] | Hubert Cochet MD, PhD[2,5] | Jean-Benoit Thambo MD, PhD[2,3] | Frederic Sacher MD, PhD[1,2]

[1]Department of Cardiac Pacing and Electrophysiology, Bordeaux University Hospital (CHU), Bordeaux, France

[2]IHU Liryc, Electrophysiology and Heart Modeling Institute, University of Bordeaux, Bordeaux, France

[3]Department of Congenital Heart Disease, Bordeaux University Hospital (CHU), Bordeaux, France

[4]University of Ottawa Heart Institute, Ottawa, Ontario, Canada

[5]Department of Radiology, Bordeaux University Hospital (CHU), Bordeaux, France

Correspondence
Benjamin Bouyer, MD, Hopital Cardiologique du Haut leveque, CHU de Bordeaux, Ave du Haut Leveque, 33604 Pessac Cedex, France.
Email: benjamin.bouyer@chu-bordeaux.fr

Disclosures: None.

Funding information
National Research Agency (ANR), Grant/Award Number: ANR-10-IAHU-04

Abstract

Aim: Ventricular arrhythmias (VAs) are the most common cause of death in patients with repaired Tetralogy of Fallot (rTOF). However, risk stratifying remains challenging. We examined outcomes following programmed ventricular stimulation (PVS) with or without subsequent ablation in patients with rTOF planned for pulmonary valve replacement (PVR).

Methods: We included all consecutive patients with rTOF referred to our institution from 2010 to 2018 aged ≥18 years for PVR. Right ventricular (RV) voltage maps were acquired and PVS was performed from two different sites at baseline, and if non-inducible under isoproterenol. Catheter and/or surgical ablation was performed when patients were inducible or when slow conduction was present in anatomical isthmuses (AIs). Postablation PVS was undertaken to guide implantable cardioverter-defibrillator (ICD) implantation.

Results: Seventy-seven patients (36.2 ± 14.3 years old, 71% male) were included. Eighteen were inducible. In 28 patients (17 inducible, 11 non-inducible but with slow conduction) ablation was performed. Five had catheter ablation, surgical cryoablation in 9, both techniques in 14. ICDs were implanted in five patients. During a follow-up of 74 ± 40 months, no sudden cardiac death occurred. Three patients experienced sustained VAs, all were inducible during the initial EP study. Two of them had an ICD (low ejection fraction for one and important risk factor for arrhythmia for the second). No VAs were reported in the non-inducible group ($p < .001$).

Conclusion: Preoperative EPS can help identifying patients with rTOF at risk for VAs, providing an opportunity for targeted ablation and may improve decision-making regarding ICD implantation.

KEYWORDS
catheter ablation, electrophysiological study, Fallot, pulmonary valve replacement, ventricular tachycardia

1 | INTRODUCTION

Patients with repaired tetralogy of Fallot (rTOF) now commonly survive into mid-adulthood as a testament to the progress made in their medical and surgical management.[1] However, their risk of sudden cardiac death (SCD) due to ventricular arrhythmias (VAs) remains high (estimated at approximately around 0.1%–0.2% per year),[2,3] and accurately estimating their arrhythmic risk is difficult.[4] Historical markers, such as QRS complex duration and patients' clinical histories, have limited predictive value.[5] Given that VAs are the leading cause of death in patients with rTOF,[5] developing tailored strategies to predict—and ideally to modify—their arrhythmic risk has the potential to markedly improve their clinical outcomes.

Invasive programmed ventricular stimulation (PVS) in patients with rTOF was first assessed by Khairy et al., suggesting its potential diagnostic and prognostic value, as well as improving our understanding of the underlying mechanisms of VA in this population.[6,7] VA are typically monomorphic, characterized by macro-reentrant circuits arising around patches and valve annuli with areas of scar and slow conduction contributing to the arrhythmic substrate and anatomical isthmuses (AI).[8,9] As the general understanding of these circuits improved, ablation strategies were used to create lines of block along critical parts of these AIs.[10]

Pulmonary valve replacement (PVR) is commonly required for pulmonic valve insufficiency in patients with rTOF and may represent an opportunity to perform an electrophysiologic study (EPS) with PVS as it could prompt additional interventions, including surgical cryoablation, implantable cardioverter-defibrillator (ICD) implantation, and correction of residual lesions.[11] Indeed, this rationale led to our center adopting a protocol of systematically performing EPS and surgical or percutaneous ventricular ablation[12] in patients with rTOF planned for PVR. We herein report the procedural and clinical outcomes of this approach.

2 | METHODS

The present research adhered to the guiding principles of the Declaration of Helsinki and has been approved by our ethics committee on human research. Nonopposition for personal data used information was addressed to the patients (CNIL, MR004). Patients did not object to the use of their personal data (regulatory authorization MR-004, CNIL). Consecutive patients aged ≥18 years with rTOF who were planned to undergo PVR and who were referred to our center between January 1, 2010, and December 12, 2018, were included. This period was selected to allow for at least 5 years of follow-up. All patients referred for PVR beneficiated from an EPS.

2.1 | Data collection

Medical records were reviewed for clinical and surgical details. ECGs were analyzed to measure QRS duration. Rhythm assessments were based on ECGs, Holter monitors, and ICD interrogations, when applicable. Cardiac magnetic resonance (CMR) and transthoracic echocardiography (TTE) studies were reviewed to determine biventricular function and volumes. The presence of established risk factors for VA were assessed, including QRS duration >180 ms, left ventricular ejection fraction (LVEF) <45%, right ventricular ejection fraction (RVEF) <35%, prior nonsustained ventricular tachycardia (NSVT), history of syncope, and prior palliative shunts.[13] These factors were considered along with the results of EPS and acute success of ablation, if applicable, in decisions regarding ICD implantation.

PREVENTION-ACHD risk score model:

We decided to incorporate the risk score model developed by Vehmeijer et al.[14] to stratify the risk of SCD in a noninvasive manner. The score was designed as follows: 7 risk factors were selected:

(1) coronary artery disease, (2) heart failure symptoms (New York Heart Association class II/III), (3) supraventricular tachycardia, (4) impaired systemic ventricular function (ejection fraction, 40% on echocardiography), (5) impaired subpulmonary ventricular function (ejection fraction, 40% on echocardiography), (6) QRS duration >120 ms, and (7) QT dispersion >70 ms. Each risk factor is attributed 1 point. Considering the Tetralogy of Fallot population a risk score <4 represent an annual risk of SCD < 3% (low-risk patients) and risk score >4 is an annual risk >3% (high-risk patient).

2.2 | Cardiac magnetic resonance

CMR was performed during the electrophysiological study (EPS) with chamber volume assessments as well as a high-resolution late gadolinium enhancement (LGE) sequence. The processing of high-resolution LGE was performed using MUSIC software (IHU Liryc, University of Bordeaux and Inria Sophia Antipolis, France).

In-plane and through-plane interpolation were applied to resample the imaging volume at a voxel size of 0.625 × 0.625 × 1 mm. Semi-automated tools were used to segment endocardial and epicardial contours of the right ventricle. Iterative histogram thresholding was applied to segment myocardial scar, the threshold being set three standard deviations above the mean intensity of normal myocardium, as measured in a normal septal area. Endocardial segmentation was used to compute a 3D surface mesh at high density (>50 000 triangles), onto which myocardial scars were projected and scar areas were measured. The ratio of total right ventricular (RV) to scar surface area was calculated.[15]

2.3 | Electrophysiologic study and right ventricular mapping

All consecutive patients addressed for PVR underwent EPS. RV endocardial map was performed to identify scar and potential isthmuses as reported previously.[6,16] Procedures were performed under local anesthesia and two introducers were placed inside the right femoral vein. We used either the Carto 3 mapping system (Biosense Webster) or the RHYTHMIA system (Boston Scientific). PVS was then performed at two drive trains (600 ms and 400 ms) and at two sites. RV maps were created during sinus rhythm or atrial pacing. Voltage maps and activation maps were analyzed to define and characterized isthmuses and zone of interest. Typically, areas of low voltage were associated with slower conduction times across the isthmus. Then we stimulated the RV outflow tract (RVOT) and RV apex, with up to three extrastimuli decrementing to the ventricular effective refractory period or 200 ms. Inducibility was defined as any ventricular arrhythmia (monomorphic ventricular tachycardia [VT], polymorphic VT, or ventricular fibrillation [VF]) lasting 30 s or longer or resulting in hemodynamic instability requiring pace-termination or defibrillation. If a patient was noninducible at baseline, the protocol was repeated during isoproterenol infusion using a 400 ms drive train with an identical extrastimuli protocole.

In patients who underwent surgical cryoablation alone or who still had inducible VAs after percutaneous ablation, an EPS with PVS and electro-anatomical mapping was repeated 3 months post-PVR to guide decisions regarding ICD implantation.

2.4 | Definition of anatomical isthmuses (AI)

Four types of AIs have been described previously in rTOF.[8,17] Type 1 is bound by the tricuspid annulus and the RV incision, RV patch, or large transannular patch. Type 2 is bound superiorly by the pulmonary valve annulus and inferiorly by the infundibular patch or RV incision. Type 3 is bordered by the ventricular septal defect patch and the pulmonary valve annulus. Type 4 is defined between the tricuspid annulus and a larger VSD patch, usually when the defect is located in the muscular region.

2.5 | Pulmonary valve replacement

In most cases, PVR was performed surgically using a prosthetic valve or a homograft sized to the annulus.[17] When anatomical and technical conditions were appropriate, transcatheter valve implantation with a Melody transcatheter pulmonary valve (Medtronic) was performed.

2.6 | Ablation

Percutaneous catheter ablation was performed in patients with inducible VAs during EPS or with slow conduction within their AIs.[13] Before induction, a mapping catheter was placed on the isthmus 3. In case of VT induction, activation mapping was attempted when possible, with entrainment performed at isthmus 3. When mapping was not achievable, ablation targeted the isthmus involved determined by pace mapping. All catheter ablations were performed either with a 4-mm-tip irrigated catheter (ThermoCool SmartTouch SF Biosense Webster) or Intellanav MiFi OI (Boston, Marlborough, MA). Point-by-point lesions radiofrequency was delivered for 30–60 s with an inter-lesion distance <4 mm, using the power control mode with the temperature limited to 45°C, and normal saline irrigation (8–20 mL). Lines of block were assessed by activation mapping.

Acute success was defined as block of the isthmus and non-inducibility under isoproterenol infusion. Ablation catheter stability was optimized using a steerable long sheath (Agilis medium or large curve, St, Jude Medical St Paul, MN). Figure 1 represents an electrical activation and voltage map (an activation map video is available in Supporting Information SV1).

Surgical cryoablation was performed when endocardial RF ablation failed to achieve isthmus block, when RF ablation was not attempted despite slow conduction in the isthmus, or when patients were still inducible after ablation. Cryoablation lesions were planned preoperatively based on review of the RV endocardial substrate map by both the electrophysiologist and the cardiac surgeon with the goal of blocking the AIs identified during the preoperative EPS as responsible for the VT or having slow conduction (conduction velocity < 0.5 m/s). Cryoablation lesions connected either the superior border of the ventricular septal defect patch to the pulmonary valve annulus or the ventriculotomy incision line to the tricuspid valve annulus. Lesions were delivered for 90–120 s at −60°C with a 15-mm probe (CryoCath, Medtronic).[11] Biderectionnal block was not assessed during surgery but at 3 months post surgery with a second EPS.

2.7 | Follow-up

Patients were assessed by members of our adult congenital heart disease and/or electrophysiology departments at their first outpatient visit. Subsequent visits could be either at other tertiary centers or with patients' cardiologists. Missing data was retrieved by phone calls and mail exchange. For the purpose of this study, follow-up started at the time of EPS and ended at last patient's contact. 24 h

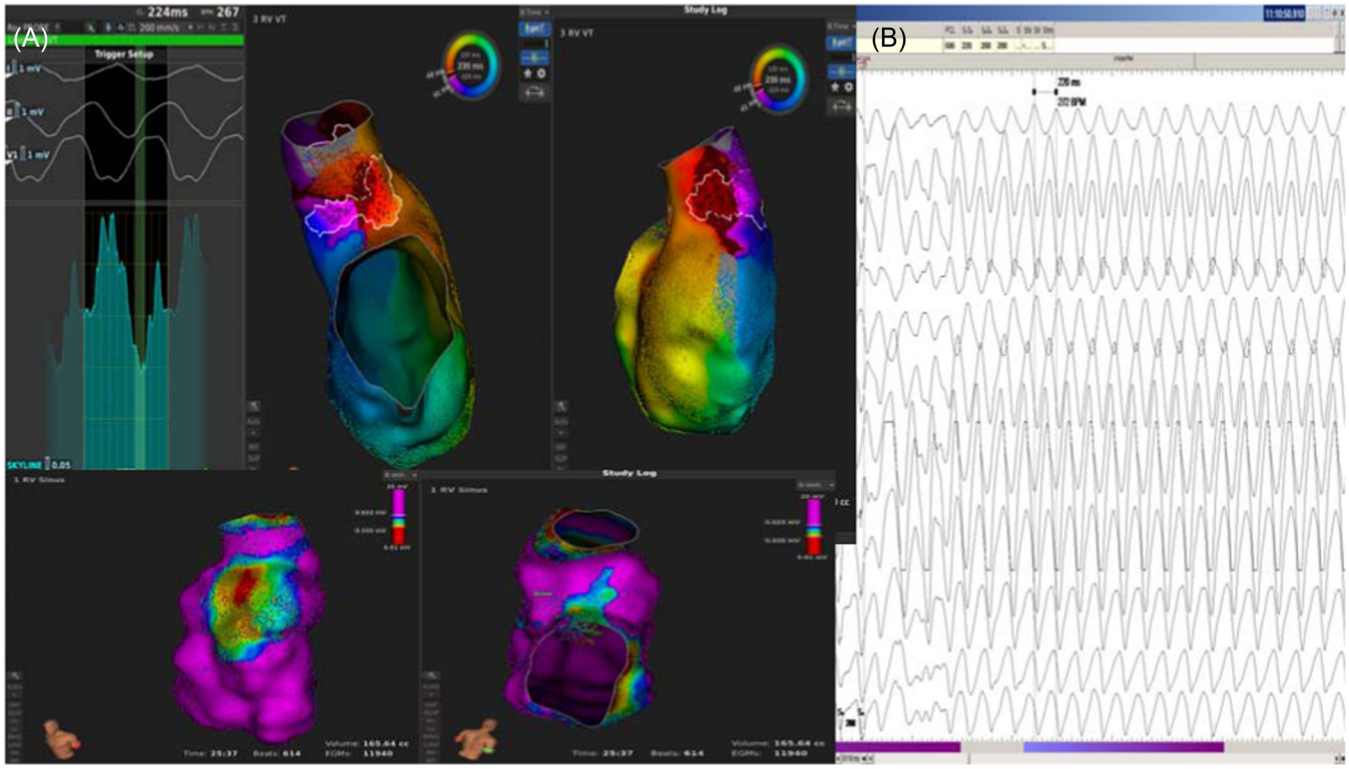

FIGURE 1 (A) The upper part shows the electro-anatomical activation mapping of the VT in which we can identify a dual loop circuit. The lower part shows the corresponding voltage map where we can identify the infundibular and VSD patches. (B) Shows the inducible VT with a cyclelength of 220 ms. VT, ventricular tachycardia.

Holter monitor recordings, ICD interrogations, or 12 lead ECG documentations were used to asses VAs. Mortality was evaluated from hospital records. The primary outcome of interest was a combined event including VT, appropriate ICD therapy, and SCD.

2.8 | Statistical analysis

Continuous non-normally distributed data are reported as median with interquartile range, normally distributed data are presented as mean ± standard deviation. Categorical data are presented as absolute numbers and percentages. Wilcoxon and Fisher's exact tests were used for comparisons, as appropriate. The occurrence of VT during follow-up was compared between inducible and non-inducible patients using a log-rank test (BiostaTGV Pierre Louis d'Epidémiologie et de Santé Publique UMR S 1136). *p*-values were two-sided and considered statistically significant if <.05.

3 | RESULTS

Seventy-seven patients with rTOF (aged 36.2 ± 14.3 years, 71% male) underwent EPS before PVR according to our protocol. The mean age at the time of their surgical repair was 4.4 ± 7.5 years, with 44% having received a transannular patch. Their mean RVEF was 42.5 ± 9.1% with an end-diastolic RV volume of 161.2 ± 41.2 mL/m^2 and LVEF of 55.8 ± 9.2% at the time of EPS. Patients who were inducible at index EPS had a greater number of arrhythmic risk factors (1.2 vs 0.5, $p = .043$) and a lower RVEF (37.8% vs. 43.6%, $p = .017$). The mean age at the time of PVR was 37.16 ± 14.3 years. Transcatheter pulmonary valve implantation was performed in 11% in both inducible and non-inducible groups. Additional clinical, imaging, and procedural details are described in Table 1.

3.1 | Noninvasive stratification using the PREVENTION ACHD score model

From the 77 patients in our cohort, five patients were identified as high-risk and 72 as low-risk using this scoring model. Among these high-risk patients only three were inducible, three patients benefited from ICD implantation (the three inducible patients). During follow-up two patients experienced VT treated by appropriate shock delivered by the ICD. In the low-risk group, 15 patients were inducible, one patient had VT during follow-up. Considering ICD implantation in this group, one inducible patient had a well-tolerated VT during follow-up and ICD implantation thereafter. The other patient was not inducible and had ICD implantation because of syncope and non-sustained VT recorded on an implantable loop recorder.

TABLE 1 Clinical and procedural details.

		Total = 77	Inducible (*n* = 18)	Non-inducible (*n* = 59)	*p*-value
General	Age (years)	36.2 ± 14.3	38.6 ± 15.6	357 ± 13.7	.459
	Male sex	55/77 (71.4%)	14/18 (77.8%)	41/59 (69.5%)	.566
	Height (cm)	167.8 ± 9.8	169.7 ± 8.2	167.2 ± 10.3	.580
	Weight (kg)	68.6 ± 18.3	70.8 ± 13.7	67.9 ± 19.5	.452
	Age at repair (years)	4.4 ± 7.5	6.4 ± 7.5	3.8 ± 5	.194
	Age at PVR (years)	37.16 ± 14.3	33.5 ± 15.4	29.1 ± 13.9	.363
	Melody valve	8/77 (10.4%)	2/18 (11%)	6/59 (11%)	1.0
	Prior shunts	27/77 (35.1%)	6/18 (33.3%)	21/59 (35.6%)	1.0
	TA patch	34/77 (44.2%)	10/18 (55.6%)	24/59 (40.7%)	.291
	Ischemic heart disease	4/77 (5.2%)	1/18 (5.5%)	3/59 (5.1%)	1.0
	No. of arrhythmic risk factors	0.69 ± 1.01	1.16 + 1.3	0.54 ± 0.9	**.0431**
	QRS duration (ms)	147.5 ± 27.6	155.6 ± 25.8	144.9 ± (27.8)	.125
TTE	E/E'	6.1 ± 2	6.1 ± 1.7	6.1 ± 2.1	.730
	sPAP (mmHg)	40.9 ± 16.2	41.2 ± 14.2	40.8 ± 16.9	.729
MRI	LVEF (%)	55.8 ± 9.2	52.8 ± 10.6	57.4 ± 9.2	.166
	RVEF (%)	42.5 ± 9.1	37.8 ± 8.3	43.6 ± 8.7	**.0169**
	Indexed RVED (mL/m^2)	161.2 ± 41.2	174.8 ± 56	156.9 ± 34.7	.143
	%Scar/total RV surface	7.9 ± 4	8.7 ± 3.5	7.9 ± 4.4	.147
	RVOT scar (cm^2)	10.2 ± 6.6	10.2 + 7.1	10.2 ± 4.4	.75
	Septal scar (cm^2)	8.1 ± 4.5	9.7 ± 5	7.6 ± 4.2	.073
	Total scar (cm^2)	19.6 ± 9.9	22.1 ± 11	18.8 ± 9.5	.09
ICD	ICD carrier	5/77 (6.5%)	4/18 (22.2%)	1/59 (1.7%)	**.009**
	Primary prevention	4/5 (80%)	3/4 (75%)	1/1 (100%)	-
	Secondary prevention	1/5 (20%)	1/4 (25%)	0 (0%)	-
	Appropriate therapy	2	2	0	-
	Inappropriate therapy	1	0	1	-
EPS/ablation	Inducibility	18/77 (24%)	100%	0%	-
	Need for isoproterenol	4/77 (5.2%)	4/18 (22.2%)	0%	-
	Inducible after ablation	5/77 (6.5%)	5/16 (31.2%)	0%	
	Repeat EPS (if inducible)	7/77 (9.1%)	7/18 (39%)	0%	-
	Inducibility at repeat EPS	0//7	0/7	0%	-
	No. patients ablated	28/77 (35%)	17/18 (95%)	11/59 (19%)	**.000**
	Catheter ablation	5/27 (18.5%)	5/17 (30%)	0/11 (0%)	.0598
	Surgical ablation	9/27 (33.3%)	2/17 (11.7%)	7/11 (63.7%)	.091
	Catheter + surgical ablation	14/27 (52%)	10/17 (59%)	4/11 (36.4%)	.440
	Total AIs targeted	31	20	11	-
	AI1	2/31 (6.4%)	2/20 (10%)	0/11 (0%)	.527
	AI2	7/31 (22.7%)	4/20 (20%)	3/11 (27.3%)	.676
	AI3	22/31 (71%)	14/20 (70%)	8/11 (72.2%)	.879

(Continues)

TABLE 1 (Continued)

	Total = 77	Inducible (n = 18)	Non-inducible (n = 59)	p-value
AI4	0/31 (0%)	0/20 (0%)	0/11 (0%)	1
Complications	0	0	0	-

Abbreviations: AI, anatomical isthmus; EPS, electrophysiological study; ICD, intracardiac defibrillator; LVEF, left ventricular ejection fraction; PVR, pulmonary valve replacement; RVED, right ventricular end-diastolic diameter indexed; RVEF, right ventricular ejection fraction; RVOT, right ventricular outflow tract; sPAP, systolic pulmonary arterial pressure; TA, transannular.

3.2 | Cardiac magnetic resonance imaging

All patients exhibited both septal and RVOT scars. Patients who were inducible during EPS tended to have larger scar areas relative to the noninducible group, however, the differences were not statistically significant. Specifically, RVOT, septal, and total scar areas were 10.2 ± 7.1 versus 10.2 ± 4.1 cm^2 (p = .75), 9.7 ± 5 versus 7.6 ± 4.2 cm^2 (p = .073), and 22.1 ± 11 versus 18.8 ± 9.5 cm^2 (p = .09) in inducible versus noninducible patients, respectively.

3.3 | Inducibility and VT ablation

From the 77 patients enrolled 18 were inducible (24%). Among inducible patients, isoproterenol was required for induction in 22%. All patients had monomorphic VT except one patient who exhibited a discrete polymorphic VT. Ablation was performed in all inducible patients except in one who underwent ICD implantation because of a clear pre-existing primary prevention indication (LVEF <35%) and left-sided VT. In comparison, 11 of 59 non-inducible patients (19%) had ablation performed, targeting slow-conducting AIs. AI type 3, the isthmus bordered by the ventricular septal defect patch and the pulmonary valve annulus was the most frequently involved in arrhythmia circuits and subsequently the most ablated (AI3: 71%; AI2: 22,7%; AI1: 6,4%; AI4: 0%). Moreover, five patients in the inducible group had two different isthmuses targeted during the RF procedure mainly because of electrophysiological properties such as slow conduction time across a define isthmus. Importantly, no complications were reported. After catheter ablation, five patients were still inducible, all of whom underwent surgical cryoablation of the targeted isthmus followed by repeat EPS three months afterward. Patients who underwent surgical cryoablation alone received a control EPS at three months as well. During the second EPS, none of these patients were inducible. The flow chart is depicted in Figure 2.

3.4 | ICD implantation

ICDs were implanted in five patients after EPS (7%). Four of these for primary prevention and one for secondary prevention. Patient 1 was inducible at baseline but was not inducible after ablation, however, he was implanted in primary prevention because of risk factors (important PVC and history of syncope). Patient 2 was inducible at baseline; no ablation was performed because VT originated from the left ventricle. An ICD was implanted because LVEF was <35% and VT inducibility. Patient 3 was inducible at baseline, and after RF ablation, due to altered ejection fraction of both ventricles ICD was implanted in primary prevention. Patient 4 was inducible at baseline but not after ablation, VT was documented 2 years after EPS, and ICD was implanted in secondary prevention, and had no recurrent arrhythmia for the duration of his follow-up (i.e., 2 years). Patient 5, the only non-inducible patient who underwent ICD implantation presented with no risk factors for arrhythmia and did not have ablation performed. NSVT was documented on an implantable loop recorder that was implanted for pre-syncope, which prompted their physicians to recommend an ICD for primary prevention (see Table 2). During follow-up, Patient 5 experienced inappropriate therapy and ultimately underwent device extraction because of a lead infection.

Since the device extraction, the patient has not experienced any syncope or documented arrhythmia thus far (i.e., 3 years).

3.5 | Clinical outcomes

During a mean follow-up of 74 ± 40 months, no sudden cardiac death occurred. Three patients inducible at the initial EPS had sustained VT versus none in the non-inducible group (p < .001, Figure 3). Importantly, VT-induced and clinical VT during follow-up did not share morphological characteristics and cycle length. Two patients were already implanted with an ICD and these episodes of sustained VT resulted in two appropriate ICD shocks. The first patient (Patient 2 in ICD section) was implanted with an ICD in primary prevention (LVEF < 35%), the episode occurred 5 years after EPS, and the VT cycle length was 250 ms and treated by an ICD shock. The second patient (Patient 3 in the ICD section) was inducible after ablation with altered ejection fraction of both ventricles and hence implanted in primary prevention. The event occurred 7 years after EPS in the setting of low potassium, VT had a cycle of 300 ms rapidly evolving in an electric storm precipitated. This electric storm was treated by multiple ICD shocks and potassium supplementation. Currently, the patient is arrhythmia free for 1 year. The third patient (Patient 4 in the ICD section) was inducible at baseline during EPS and noninducible after ablation (at baseline and under isoproterenol). VT was reported 2 years after his EPS. The VT was well tolerated,

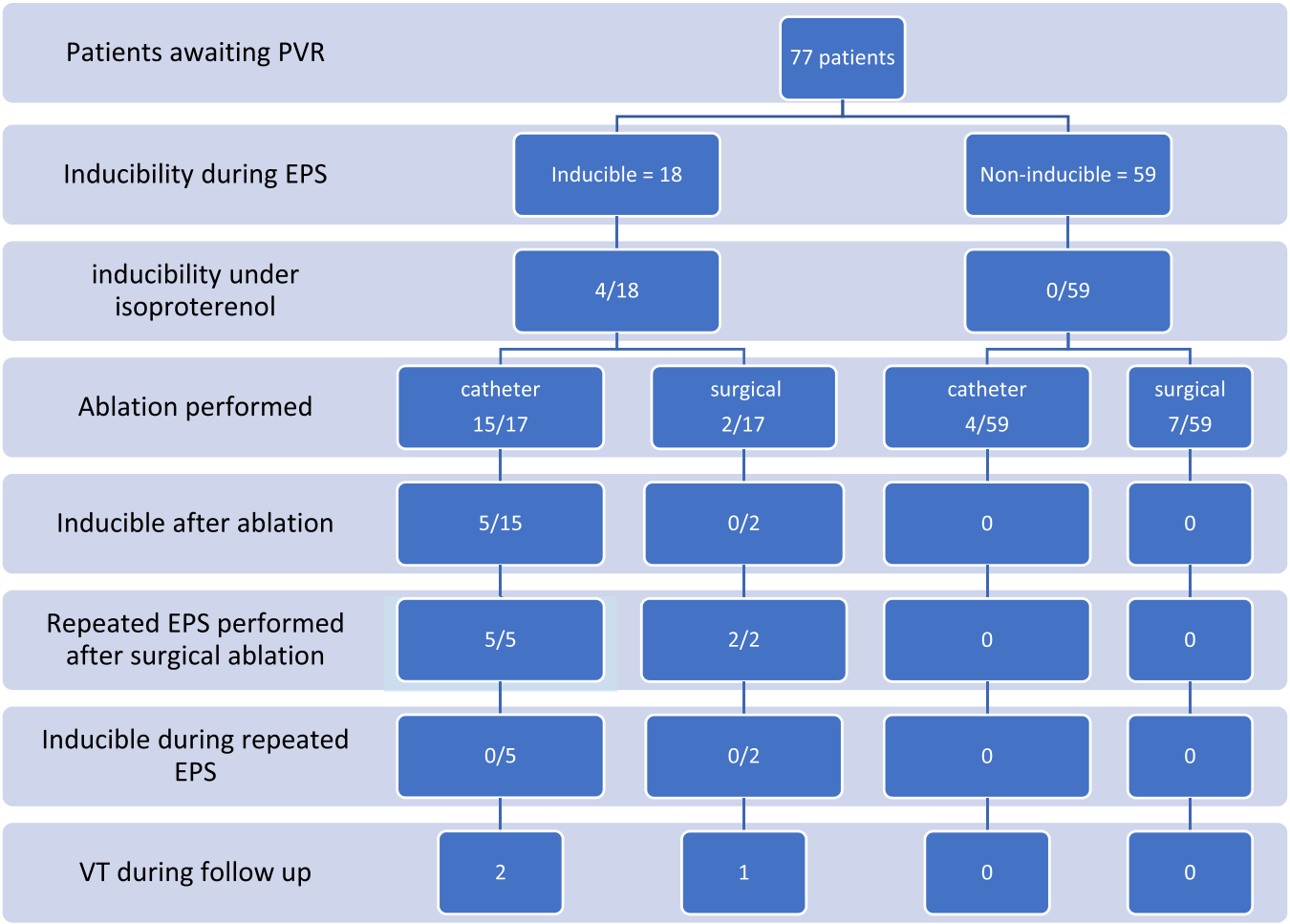

FIGURE 2 Flow chart of all patients undergoing electrophysiological study before pulmonary valve replacement. EPS, electrophysiological study.

TABLE 2 Summary of ICD implantation indications.

Patient number	EPS	Ablation	Inducibility after ablation	Risk Factors	Prevention	VT during follow-up
Patient 1	Inducible at baseline	RF + Cryo	No	Syncope and PVC	Primary	No
Patient 2	Inducible at baseline	Not performed	Not performed	LVEF <35%	Primary	Yes
Patient 3	Inducible under isoproterenol	RF	Yes	LVEF 40% RVEF 25%	Primary	Yes
Patient 4	Inducible at baseline	RF	No	None	Secondary	Yes
Patient 5	Noninducible	Not performed	Not performed	NsVT on loop recorder	Primary	No

Abbreviations: Cryo, cryoablation; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NsVT, nonsustained ventricular tachycardia; PVC, premature ventricular complex; RF, radiofrequency ablation; RVEF, right ventricular ejection fraction; VT, ventricular tachycardia.

with a cycle length of 400 ms. He benefited from an ablation and ICD implantation. He has now been free from any arrhythmia for 2 years.

One noninducible patient with an ICD experienced inappropriate anti-tachycardia pacing for atrial flutter (Patient 5 in the ICD implantation section).

4 | DISCUSSION

In this study of 77 consecutive patients with rTOF who systematically underwent EPS before planned PVR, 18 (24%) had inducible VAs. VT was monomorphic except from one patient who exhibited a

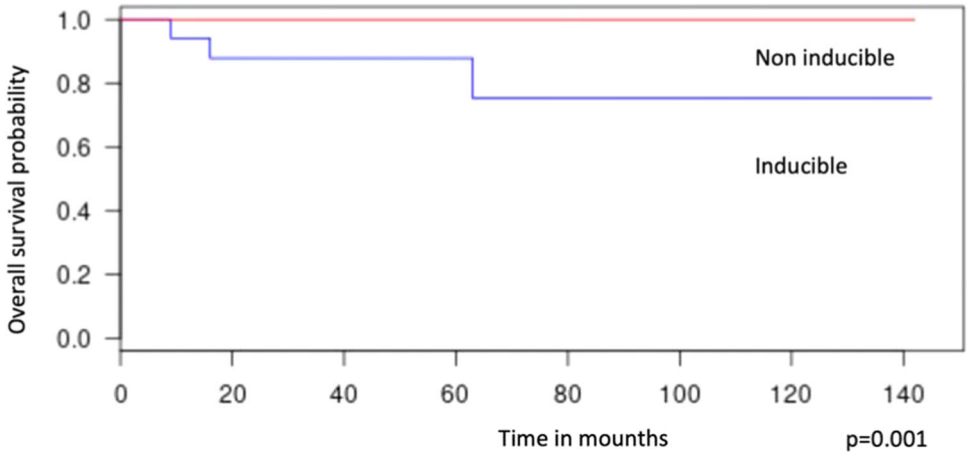

FIGURE 3 Freedom from ventricular arrhythmia among patients who were noninducible (red) and inducible (blue) at the index electrophysiologic study.

discrete polymorphic VT. All but one of these patients underwent catheter or surgical ablation and achieved noninducibility at the end of the procedure. During a mean follow-up of 74 ± 40 months, sustained VT occurred in three inducible patients.

Proposed clinical risk factors for arrhythmic complications in patients with rTOF have limited predictive value. Recently, newer risk score models were proposed to guide ICD implantation, such as the PREVENTION ACHD model which classified five patients at high risk from whom two had VT during follow-up. As first reported by Khairy et al.,[6] EPS may serve as an additional tool for risk stratification. It is important to note that the coupling interval of the last extra stimulus in our stimulation protocol was 200 ms, which is different from that used by the Khairy group, who used an interval of up to 180 ms. This difference in the protocol could result in an underestimation of the number of patients and the number of polymorphic tachycardias. However, we implemented this tool as part of the preoperative work-up in patients requiring PVR. The rationale for this was that the time immediately pre-PVR could represent a particularly vulnerable period for VAs, given the hemodynamic stresses on the RV, thus potentially increasing the sensitivity of PVS. It could also be an opportunity to perform an EPS since if catheter ablation is needed but fails to block an isthmus, surgical cryoablation at the time of PVR can be pursued.

Ablation strategies have been refined throughout the last years as our understanding of the interplay between arrhythmic mechanisms and disease-specific substrates has improved. Reentrant circuits in patients with rTOF are relatively well defined, demarcated by anatomical barriers such as valve annuli, surgical incisions, and surgical patches that provide regions of slow conduction and AIs necessary to sustain VAs.[17,18]

Indeed, Kapel GF et al.[13] demonstrated that slow-conducting AIs (defined by a conduction velocity index <0.5 m/s) were involved in all documented and inducible VT in their rTOF study population. Given that, ablation of AIs has been shown to be an effective approach with favorable outcomes and few complications,[19] as per our protocol, when patients were inducible, ablation targeting culprit or slow conducting AIs was recommended. In our experience, AI type 3 was most often targeted, probably because this AI is present in all patients with rTOF as it is a product of correcting a defining lesion of TOF (this AI arises between the site of the ventricular septal defect and the pulmonary valve annulus).

If patients were still inducible after catheter ablation, surgical cryoablation was used to complete ablation lines. Our approach, therefore, requires close collaboration between surgeons and electrophysiologists to ensure that ablation lines are guided by EPS and to maximize the likelihood that they are effectively completed as non-transmural lines can be proarrhythmic, creating the substrate they are intended to eliminate.[8] For this reason, we systematically performed repeat EPS and mapping in patients requiring surgical cryoablation, all of which confirmed linear block and non-inducibility.

Recommendations for implanting ICDs in patients with rTOF for primary prevention of VAs are based on limited evidence. The expected and potential benefits of ICDs must be balanced against the risk of inappropriate shocks, lead failure, and infection.[20,21] Our workflow provides helpful information to assist with these decisions in the future. In our study, only four patients ultimately had ICDs implanted for primary prevention based on VA inducibility during EPS and acute ablation success, in addition to established arrhythmic risk factors. Interestingly, one patient had a discrete polymorphic VT at induction, maybe because of the implication of two different isthmuses in the tachycardia circuit. The patient was not inducible after ablation and at control EPS justifying not to implant an ICD. One additional patient had an ICD implanted for secondary prevention. During follow-up, three episodes of VT were documented, all in the inducible group, with the single patient in the noninducible group experiencing inappropriate device therapy. Indeed, patients with recurrences were all inducible (2 at baseline 1 under isoproterenol), one patient had LVEF <35% known as a predictor of VA, one patient was inducible after ablation and benefited from ICD implantation and had VT during follow-up in a context of low potassium blood level. The last one had a slow VT, well tolerated during follow-up despite

ablation. All the patients presented with VA during follow-up had specific risk factors such as low LVEF or inducibility after ablation that was indicative of a higher risk of arrhythmias. One patient with no risk factor exhibited a well-tolerated slow VT, he had no specific risk factors, the score model classified him as low risk, and inducibility was the only factor identifying an increased risk for VAs. It is of paramount importance to identify this population at high risk and EPS should be performed at baseline and under isoproterenol infusion not to miss important data. Our protocol is close to that of Sandhu et al.[12]

In fact, we were able to include a similar number of patients (77 vs. 70) with a similar mean follow-up of 72 months versus 74 months in our cohort. (i.e., 6 years). We report a smaller number of inducible patients (18 vs. 34) but the same number of VT during follow-up. However, we report fewer inducible patients after ablation and, therefore, less ICD implantation (5 vs. 14). Such differences can be explained by a better definition of pathological isthmuses by voltage mapping, which was not realized by Sandhu et al. Likewise, close collaboration between surgeon and electrophysiologist made it possible to target only pathological isthmus avoiding being arrhythmogenic by carrying out unnecessary ablation lines. This different approach might have allowed us to improve our implantation decision process. However, one can imagine other factors. Systematic EPS before PVR seems to be an efficient approach to selecting patients at risk for VAs. Some authors report that PVR in itself reduces the burden of arrhythmia by decreasing the volume and pressure of the right ventricle. However, we must remain cautious, since the substrate is still present in these patients, and it is, therefore, important to associate PVR with preemptive ablation.[22,23]

It is important to specify that only patients in the inducible group experienced VT despite ablation and acute isthmus block. Therefore, a systematic control assessing isthmus block 3–6 months after the procedure might be recommended, especially if the patient was inducible before ablation and no ICD was implanted.

5 | LIMITATIONS

Our study has important limitations. The small number of events limit the strength of our conclusion. Referral bias could also have influenced our results. In our population, the average age at repair of TOF is quite old compared to the current population, which exhibits a lower risk. However, all patients referred for PVR had an EPS before, which helps reduce selection bias.

6 | CONCLUSION

Performing systematically EPS in patients with rTOF planned for PVR may help identifying patients at higher risk of VA. Ablation of culprit or slow-conducting AIs, either by catheter ablation at the time of EPS or surgical cryoablation at the time of PVR, is feasible and safe. In our study, inducibility after ablation was associated with medium-term arrhythmic complications, suggesting it may be a helpful marker of patients who may benefit from ICD implantation.

ACKNOWLEDGMENTS

This study received financial support from the French Government as part of the "Investments in the Future" program managed by the National Research Agency (ANR), Grant reference ANR-10-IAHU-04.

ORCID

Benjamin Bouyer http://orcid.org/0000-0002-7702-7610
F. Daniel Ramirez http://orcid.org/0000-0002-4350-1652
Ciro Ascione http://orcid.org/0000-0002-7735-4056
Masaaki Yokoyama http://orcid.org/0000-0003-0890-4189
Marine Arnaud http://orcid.org/0000-0003-0950-2624

REFERENCES

1. Maury P, Sacher F, Rollin A, et al. Ventricular arrhythmias and sudden death in tetralogy of Fallot. *Arch Cardiovasc Dis*. 2017;110(5):354-362. doi:10.1016/j.acvd.2016.12.006
2. Probst J, Diller GP, Reinecke H, et al. Prevention of sudden cardiac death in patients with tetralogy of Fallot: risk assessment and long term outcome. *Int J Cardiol*. 2018;269:91-96. doi:10.1016/j.ijcard.2018.06.107
3. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *JACC*. 1998;32(1):245-251. doi:10.1016/S0735-1097(98)00187-9
4. Khairy P, Aboulhosn J, Gurvitz MZ, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation*. 2010;122(9):868-875. doi:10.1161/CIRCULATIONAHA.109.928481
5. Bricker JT. Sudden death and tetralogy of Fallot risks, markers, and causes. *Circulation*. 1995;92(2):158-159.
6. Khairy P, Landzberg MJ, Gatzoulis MA, et al. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. *Circulation*. 2004;109(16):1994-2000. doi:10.1161/01.CIR.0000126495.11040.BD
7. Khairy P. Programmed ventricular stimulation for risk stratification in patients with tetralogy of Fallot: a Bayesian perspective. *Nat Clin Pract Cardiovasc Med*. 2007;4(6):292-293. doi:10.1038/ncpcardio0882
8. Moore JP, Seki A, Shannon KM, Mandapati R, Tung R, Fishbein MC. Characterization of anatomic ventricular tachycardia isthmus pathology after surgical repair of tetralogy of Fallot. *Circ: Arrhythm Electrophysiol*. 2013;6(5):905-911. doi:10.1161/CIRCEP.113.000450
9. Kapel GFL, Reichlin T, Wijnmaalen AP, et al. Re-entry using anatomically determined isthmuses: a curable ventricular tachycardia in repaired congenital heart disease. *Circ: Arrhythm Electrophysiol*. 2015;8(1):102-109. doi:10.1161/CIRCEP.114.001929
10. Zeppenfeld K, Wijnmaalen AP. Clinical aspects and ablation of ventricular arrhythmias in tetralogy of Fallot. *Cardiac Electrophysiol Clin*. 2017;9(2):285-294. doi:10.1016/j.ccep.2017.02.010
11. Caldaroni F, Lo Rito M, Chessa M, et al. Surgical ablation of ventricular tachycardia in patients with repaired tetralogy of Fallot. *Eur J Cardiothorac Surg*. 2019;55(5):845-850. doi:10.1093/ejcts/ezy407
12. Sandhu A, Ruckdeschel E, Sauer WH, et al. Perioperative electrophysiology study in patients with tetralogy of Fallot undergoing pulmonary valve replacement will identify those at high risk of subsequent ventricular tachycardia. *Heart Rhythm*. 2018;15(5):679-685. doi:10.1016/j.hrthm.2018.01.020

13. Kapel GF, Sacher F, Dekkers OM, et al. Arrhythmogenic anatomical isthmuses identified by electroanatomical mapping are the substrate for ventricular tachycardia in repaired tetralogy of Fallot. *Eur Heart J*. 2017;38(4):268-276. doi:10.1093/eurheartj/ehw202
14. Vehmeijer JT, Koyak Z, Leerink JM, et al. Identification of patients at risk of sudden cardiac death in congenital heart disease: the PRospEctiVE study on implaNTable cardIOverter defibrillator therapy and sudden cardiac death in adults with congenital heart disease (PREVENTION-ACHD). *Heart Rhythm*. 2021;18(5):785-792. doi:10.1016/j.hrthm.2021.01.009
15. Cochet H, Iriart X, Allain-Nicolaï A, et al. Focal scar and diffuse myocardial fibrosis are independent imaging markers in repaired tetralogy of Fallot. *Eur Heart J- Cardiovasc Imaging*. 2019;20(9):990-1003. doi:10.1093/ehjci/jez068
16. Kapel GFL, Brouwer C, Jalal Z, et al. Slow conducting Electro-anatomic Isthmuses. *JACC: Clini Electrophysiol*. 2018;4(6):781-793. doi:10.1016/j.jacep.2018.02.002
17. Zeppenfeld K, Schalij MJ, Bartelings MM, et al. Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus. *Circulation*. 2007;116(20):2241-2252. doi:10.1161/CIRCULATIONAHA.107.723551
18. Stevenson WG, Delacretaz E, Friedman PL, Ellison KE. Identification and ablation of macroreentrant ventricular tachycardia with the CARTO electroanatomical mapping system. *Pacing Clin Electrophysiol*. 1998;21(7):1448-1456. doi:10.1111/j.1540-8159.1998.tb00217.x
19. Laredo M, Frank R, Waintraub X, et al. Ten-year outcomes of monomorphic ventricular tachycardia catheter ablation in repaired tetralogy of Fallot. *Arch Cardiovasc Dis*. 2017;110(5):292-302. doi:10.1016/j.acvd.2017.01.009
20. Egbe AC, Miranda WR, Madhavan M, et al. Cardiac implantable electronic devices in adults with tetralogy of Fallot. *Heart*. 2019;105(7):538-544. doi:10.1136/heartjnl-2018-314072
21. Egbe AC, Vallabhajosyula S, Akintoye E, Deshmukh A. Cardiac implantable electronic devices in adults with tetralogy of Fallot. *Am J Cardiol*. 2019;123(12):1999-2001. doi:10.1016/j.amjcard.2019.03.010
22. Bessière F, Gardey K, Bouzeman A, et al. Impact of pulmonary valve replacement on ventricular arrhythmias in patients with tetralogy of Fallot and implantable cardioverter-defibrillator. *JACC: Clin Electrophysiol*. 2021;7(10):1285-1293. doi:10.1016/j.jacep.2021.02.022
23. Karamlou T, Silber I, Lao R, et al. Outcomes after late reoperation in patients with repaired tetralogy of Fallot: the impact of arrhythmia and arrhythmia surgery. *Ann Thorac Surg*. 2006;81(5):1786-1793. doi:10.1016/j.athoracsur.2005.12.039

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bouyer B, Jalal Z, Daniel Ramirez F, et al. Electrophysiological study prior to planned pulmonary valve replacement in patients with repaired tetralogy of Fallot. *J Cardiovasc Electrophysiol*. 2023;34:1395-1404. doi:10.1111/jce.15940