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Original Article

The Role of Ablation in Prevention of Recurrent Implantable Cardioverter Defibrillator Shocks in Patients With Tetralogy of Fallot

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ABSTRACT

Background: Implantable cardioverter defibrillators (ICDs) are effective in preventing arrhythmic sudden cardiac death in patients with tetralogy of Fallot (TOF). Although ICD therapies for malignant ventricular arrhythmias can be life-saving, shocks could have deleterious consequences. Substrate-based ablation therapy has become the

RÉSUMÉ

Contexte : Les défibrillateurs cardioverteurs implantables (DCI) sont efficaces pour prévenir la mort cardiaque subite provoquée par une arythmie chez les patients présentant une tétralogie de Fallot (TF). Bien que le traitement des arythmies ventriculaires malignes par DCI puisse sauver des vies, les chocs administrés peuvent avoir des con-

Ventricular arrhythmia (VA) is a well known late complication after surgical repair of a variety of congenital heart diseases (CHDs). Previous reports showed that up to 23% of deaths in adult patients with CHD were due to sudden cardiac death (SCD).[1] Repaired tetralogy of Fallot (TOF) is the most prevalent and extensively studied cyanotic CHD associated with VA.[2] Since the first reported sudden death in 1975,[3] SCD has been identified as a major cause of mortality in patients with repaired TOF, accounting for up to half of all-cause mortality.[4,5] Secondary prevention with implantable cardioverter defibrillators (ICDs) is a class I recommendation in patients with sustained VA or resuscitated cardiac arrest.[5,6] The risk of recurrent VA in these patients is higher[7] and prevention of recurrence is challenging. ICD therapies do not prevent recurrent VA, and ICD shocks are thought to be associated with increased mortality and impairment in quality of life.[8] Furthermore, ICDs have not been shown to provide absolute protection against arrhythmic sudden death.[7,9] Amiodarone is the most commonly used antiarrhythmic therapy for VA in the presence of structural heart disease.[10] However, the role of β-blockers and amiodarone in preventing ICD shock in this group of patients is limited.[7] Long-term use of amiodarone is also limited by a significantly high risk of noncardiac side effects in the young population with adult CHD.[11]

Previous reports have shown that prophylactic substrate-based radiofrequency catheter ablation (RFCA) reduced the incidence of ICD therapy for the secondary prevention of SCD in patients with a history of myocardial infarction.[12] Like

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Ethics Statement: Research ethics approval was provided by Toronto General Hospital research ethics board. The report adhered to the relevant ethical guidelines.

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standard of care to prevent recurrent ICD shocks in patients with ischemic cardiomyopathy. However, the efficacy and safety of this invasive therapy in the prevention of recurrent ICD shocks in patients with TOF has not been well evaluated.

Methods: Records of a total of 47 consecutive TOF patients (mean age: 43.1 ± 13.2 years, male sex: n = 34 [72.3%]) who underwent ICD implantation for secondary prevention between 2000 and 2018 were reviewed.

Results: Twenty (42.6%) patients underwent invasive therapy (radiofrequency catheter ablation, n = 8; surgical ablation with pulmonary valve replacement, n = 12) before ICD implantation. Twenty-seven patients (57.4%) were managed noninvasively. During follow-up (median 80.5 [interquartile range, 28.5-131.0] months), 2 (10.0%) patients in the invasive group and 10 (37.0%) patients in the noninvasive group received appropriate ICD shocks ($P = 0.036$). Logistic regression analysis showed that invasive therapy was associated with a decreased risk of ICD shocks by 81.1% (odds ratio, 0.189; 95% confidence interval, 0.036-0.990; $P = 0.049$). Furthermore, invasive therapy was associated with decreased risk of the composite outcomes of ICD shock, death, cardiac transplantation, and hospital admission (odds ratio, 0.090; 95% confidence interval, 0.025-0.365; $P = 0.013$) compared with noninvasive therapy.

Conclusions: Invasive substrate modification therapy was associated with a lower likelihood of ICD shocks and improvement of long-term outcomes in TOF patients.

séquences délétères. L'ablation du substrat est devenue le traitement de référence pour prévenir l'administration à répétition de chocs par DCI chez les patients atteints d'une cardiomyopathie ischémique. L'efficacité et l'innocuité de ce traitement invasif pour prévenir l'administration de chocs répétés chez les patients présentant une TF n'ont toutefois pas été bien évaluées.

Méthodologie : Nous avons examiné les cas consécutifs de 47 patients présentant une TF (âge moyen : 43,1 ± 13,2 ans; hommes : n = 34 [72,3 %]) ayant reçu un DCI en prévention secondaire entre 2000 et 2018.

Résultats : Au total, 20 (42,6 %) patients ont subi un traitement invasif (ablation par cathéter par radiofréquence, n = 8; ablation chirurgicale et remplacement de la valve pulmonaire, n = 12) avant l'implantation d'un DCI. Vingt-sept patients (57,4 %) ont été pris en charge de façon non invasive. Au cours de la période de suivi (durée médiane de 80,5 [intervalle interquartile : 28,5 à 131,0] mois), 2 (10,0 %) patients du groupe ayant subi une intervention invasive et 10 (37,0 %) patients du groupe ayant subi une intervention non invasive ont reçu un choc approprié par DCI ($p = 0,036$). Les résultats de l'analyse par régression logistique montrent que le traitement invasif est associé à une réduction du risque de choc par DCI de 81,1 % (rapport des cotes : 0,189; intervalle de confiance à 95 % : de 0,036 à 0,990; $p = 0,049$). En outre, le traitement invasif est associé à une réduction du risque de survenue d'un des événements du paramètre d'évaluation composé, soit un choc administré par DCI, le décès, une transplantation cardiaque ou une hospitalisation (rapport des cotes : 0,090; intervalle de confiance à 95 % : de 0,025 à 0,365; $p = 0,013$) par rapport au traitement non invasif.

Conclusions : La modification invasive du substrat a été associée à une probabilité plus faible de choc administré par DCI et à une amélioration des résultats à long terme chez les patients présentant une TF.

ischemic heart disease, ventricular tachycardia (VT) in patients with repaired TOF results from macro reentry.[13] The occurrence of VT in the absence of left ventricular (LV) dysfunction in a significant percentage of TOF patients suggests the involvement of the right ventricle (RV) in VT circuit formation.[14] Right ventricular scar,[15-17] especially around the right ventricular outflow tract (RVOT) incision/patch and around the ventricular septal defect (VSD) patch[13-16] play a crucial role in substrate formation. The anatomical isthmuses (AIs) in TOF patients are full-thickness unlike subendocardial isthmuses in ischemic substrates or epi/mesocardial in nonischemic substrates.[5,10] However, transecting AIs with RFCA during sinus rhythm is reported to be effective in the management of VA in TOF patients.[14,17] Pulmonary valve replacement (PVR) with surgical cryoablation (SA) is also effective in decreasing arrhythmic risk.[18,19] However, little is known about the efficacy and safety of invasive therapy including RFCA and SA in the prevention of recurrent ICD shock in patients with repaired TOF. The aim of this study was to examine the effect of RFCA and SA on the reduction of the first ICD shock in secondary-prevention ICD recipients with repaired TOF.

Methods

Patient population and study design

Records of adult patients (age older than 18 years) with repaired TOF who underwent initial ICD/implantable cardiac resynchronization therapy defibrillator (CRT-D) placement for secondary prevention at Toronto General Hospital between 2000 and 2018 were retrospectively reviewed. After obtaining ethics approval from the University Health Network research review board, medical records of all patients were examined for clinical presentations, baseline characteristics, procedural details, device implantation, and follow-up.

Patients who underwent surgical ablation with PVR or radiofrequency ablation before ICD implantation were identified as the invasive therapy group. Electrophysiological study (EPS) before ICD implantation and surgical PVR was dependent on the decision of the treating cardiologist. However, patients with unstable hemodynamic conditions during index arrhythmic events were excluded from EPS. Indications for PVR before ICD/CRT-D implantation were also noted.

EPS and ablation procedure

EPS and RFCA were performed with the patient under conscious sedation or general anaesthesia. VT induction was attempted with extrastimuli at 2 different drive trains (600 and 400 ms) with 3-5 extrastimuli delivered at twice-diastolic threshold or burst pacing from the RV apex and the RVOT. If the induced VT was hemodynamically stable, activation mapping was attempted during VT using the CARTO system (Biosense Webster, Irvine, CA). The critical isthmus of VT was defined as the location where entrainment mapping (pacing cycle length 20-30 ms shorter than tachycardia cycle

length) produced concealed entrainment and the post pacing interval was less than 30 ms of the tachycardia cycle length. Substrate mapping with electroanatomical mapping was performed in all patients in sinus rhythm. Bipolar intracardiac electrogram recordings were displayed and stored on a computer-based amplifier system (Prucka Systems, GE Healthcare, Piscataway, NJ). The electrogram voltage amplitude of less than 1.5 mV was considered abnormal/diseased tissue. Areas with low-amplitude electrograms less than 0.5 mV with a pacing threshold of more than 10 mA were tagged as electrically unexcitable scar. Regions of abnormal electrograms (fractionated electrogram, isolated potentials, and late potentials) were also identified. If pacing from an area reproduced the clinical VT morphology, it was considered as the VT exit site. ThermoCool catheters (3.5-mm tip, interelectrode spacing 2 mm; SmartTouch, Biosense Webster) with contact force technology and multielectrode catheters were used for activation and voltage mapping, if available. The power output was 30-35 W and the temperature limited to 45°C, aiming for contact force in the range of 10-20*g*. Whenever possible, conduction block across an isthmus was confirmed using differential pacing and mapping. Conduction block could not be checked in all patients because of anatomic constraints. Complete procedural success was defined as noninducibility of any VT and transection of the critical anatomic isthmuses.

Surgical procedure

Surgical PVR. The indications for PVR were: (1) moderate to severe pulmonary regurgitation; (2) exercise intolerance; and (3) progressive right ventricular dilation.[20] Additional procedures such as tricuspid valve annuloplasty and atrial septal defect/VSD repair were performed if needed.

Surgical ablation. The objective of surgical ablation was to eliminate possible areas of slow conduction[13] using cryoablation during surgical PVR. The freezes were performed for 90-120 seconds each at −60° Celsius with a 15-mm probe (CryoCath; Medtronic, Montreal, Quebec, Canada). Ablation sites were decided using preoperative substrate mapping or intraoperative mapping during surgery. The details of intraoperative mapping were described previously.[21] In brief, intraoperative mapping was performed using a custom RV balloon electrode array for recording endocardial activation and a second electrode array positioned over the surface of the heart for epicardial recording. Induction of VT was performed using a standard pacing protocol from the RV apex. For patients without operative mapping or EPS, empirical cryoablation was performed as previously described.[18] The AIs were defined as follows: AI 1 in between RVOT incision or patch and tricuspid annulus (TA), AI 2 by an RVOT incision to pulmonary valve annulus (PV), AI 3 by VSD patch and PV, and AI 4 by VSD patch and TA.[13,14] The AIs are described in Figure 1A.

Patient evaluation and ICD information

All patients were evaluated in the outpatient clinic at 1 month after implantation. Patients were then followed-up at 3- to 6-month intervals. Clinical evaluation and device testing were carried out at each follow-up visit. Follow-up data from the outpatient clinic were evaluated for appropriate ICD shocks. ICD shocks were classified into those due to monomorphic VT, polymorphic VT, and ventricular fibrillation (VF).[7] Data on inappropriate ICD shocks were also noted. Inappropriate ICD shocks were also classified as per most probable underlying mechanisms (lead malfunction, atrial fibrillation, sinus tachycardia, atrial tachycardia or flutter).[14]

Programming was individualized, and parameters were tailored according to the documented cycle length of clinical VAs. In patients with recorded clinical VT, the VT zone was programmed 10-20 bpm slower than clinical VT. For patients with unknown VT cycle length, VT detection was programmed at rates higher than 187 bpm with the delivery of 3 predefined sequences of antitachycardia pacing followed by maximal energy shock. VF detection was activated above 230 bpm with antitachycardia pacing while charging, followed by maximal energy shock. The number of intervals to detect VT/VF was programmed to 18 of 24 in all patients.

Outcome analysis

The purpose of this study was to evaluate the efficacy of invasive substrate modification therapy (RFCA and SA with PVR) before ICD implantation in the prevention of recurrent ICD shocks in TOF patients with secondary ICD/CRT-D implantation. The primary outcome variable was first appropriate ICD shock after device implantation. We also evaluated composite outcomes, which include death, heart transplantation, heart failure, and appropriate ICD shock after device implantation.

Statistical analysis

Continuous variables are expressed as mean ± SD or median and interquartile range (IQR) and were compared between groups using Student *t* test or rank sum test. Categorical variables are expressed as numbers and proportions and were compared using the χ^2 test. To identify the predictors of ICD shock, logistic regression analysis was used because of the small number of events and study population. Results are reported in odds ratios (OR) with 95% confidence intervals (CIs). All tests were performed using SPSS 26.0 software Mac OS version (IBM Corp, Armonk, NY). Values of $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

A total of 47 consecutive TOF patients (n = 34 [72.3%] male and mean age 43.1 ± 13.2 years) were included in the study. The median follow-up period was 85.0 (IQR, 28.5-131.0) months. Indications for ICD implantation were cardiac arrest (VA or cardiac arrest requiring cardiopulmonary resuscitation) in 14 (29.8%) and sustained VT in 33 (70.2%) patients as index arrhythmia events. No patient in the invasive therapy group received CRT-D. Six patients in the noninvasive therapy received CRT-D. The indication in 1 patient was complete heart block with moderate LV dysfunction (LV ejection fraction [LVEF] > 35%). The other 5 patients underwent CRT-D implantation because of LV dysfunction

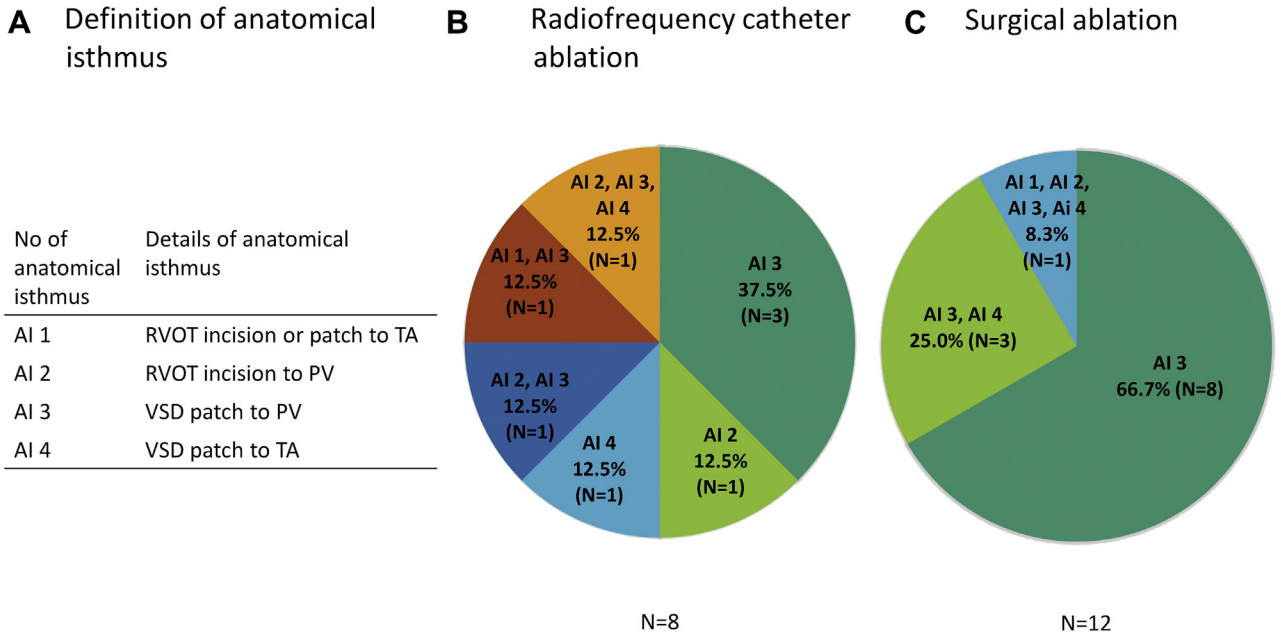

Figure 1. (**A**) Definition of anatomical isthmus and details of ablation therapy: (**B**) radiofrequency catheter ablation, and (**C**) surgical ablation. AI, anatomical isthmus; PV, pulmonary valve; RVOT, right ventricular outflow tract; TA, tricuspid annulus; VSD, ventricular septal defect.

(LVEF < 35%) and a wide QRS complex. The mean age at total repair was 8.5 ± 7.4 years. The transannular patch was used in 27 (57.4%) patients and the transventricular approach was used in 25 (53.2%) patients. The mean LVEF obtained using echocardiogram and magnetic resonance imaging was 49.8 ± 14.4% and 49.0 ± 10.9%, respectively. Baseline characteristics are summarized in Table 1. Twenty-eight patients underwent diagnostic EPS before ICD implantation. VT/VF was induced in 20 (71.4%) patients. Characteristics of the noninvasive and invasive group patients are also shown in Table 1.

Procedure details and acute outcomes of invasive therapy

A total of 20 (42.6%) patients underwent invasive therapy before device implantation. Eight (17.4%) patients underwent RFCA before device implantation. In the RFCA group, VA was induced in 6 (75%) patients, with a mean cycle length of 253.3 ± 37.2 ms. Activation mapping/entrainment mapping could not be performed in 4 cases because of hemodynamic instability during VT. Only 2 patients (25%) tolerated induced VT to permit mapping. Six patients (75.0%) received ablation from the VSD patch to PV (AI 3), 1 patient (number 7; 12.5%) received ablation from the RVOT incision to TA (AI 1), and 1 patient (number 5; 12.5%), with history of ablation from VSD patch to PV received ablation from VSD patch to TA (AI 4). Among the patients who underwent ablation from the VSD patch to PV (n = 6), 1 patient (number 3) received additional ablation from RVOT incision to PV (AI 2), and 1 patient (number 4) received ablation from RVOT incision to PV and VSD patch to TA. One patient (number 8) underwent ablation from RVOT incision to PV (AI 2). Cavotricuspid isthmus (CTI) ablation was performed in 1 (14.3%) patient (number 1). No complication occurred after RFCA. Details of ablation sites and patient data are shown in Figure 1B and Supplemental Table S1.

Twelve (25.5%) patients underwent SA at the time of PVR. In 5 (41.7%) patients, additional surgical procedures were performed at the time of surgery. In 4 patients (33.3%) ablation was guided by previous substrate mapping, 4 patients (33.3%) underwent intraoperative mapping, and ablation was empiric in 4 patients (33.3%). All patients received cryoablation from the VSD patch to PV (AI 3). Three patients (numbers 4, 9, and 12; 25%) received additional ablations from the VSD patch to TA (AI 4) and 1 patient (number 1; 8.3%) received ablation in all 4 AI. Three patients (numbers 1, 4, and 10; 25.0%) received additional substrate ablation using RFCA during preoperative mapping. CTI ablation was performed in 2 patients (numbers 3 and 11; 16.7%). Right atrial cryo maze was performed in 1 patient (number 9; 8.3%). No life-threatening complications including VA occurred during perioperative periods. Details of patients with SA are shown in Supplemental Table S2.

Appropriate ICD shocks

A total of 12 patients (25.5%) received appropriate ICD shocks during follow-up, with an annual incidence of 4.6% per year. Ten patients (83.3%) received shock because of monomorphic VT (311 ± 55 ms), 1 patient (8.3%) because of true VF, and another patient (8.3%) because of pulseless VT. The cumulative incidence of appropriate ICD shock in invasive therapy (n = 2; 10.0%) was significantly lower than that of noninvasive therapy (n = 10; 37.0%; $P = 0.034$; Fig. 2). The annual incidence of appropriate ICD shocks in the invasive and noninvasive therapy group were 2.3% and 5.8% per year, respectively. Two patients in the CRT-D group received appropriate ICD shocks. However, the benefit of invasive therapy persisted even after excluding

Table 1. Patient characteristics according to the therapies before device implantation in the noninvasive and invasive groups

	Total (N = 47)	Noninvasive therapy (n = 27)	Invasive therapy (n = 20)	*P*
Age at device implantation, years	43.1 ± 13.2	44.0 ± 14.2	42.0 ± 11.8	0.603
Male sex, n, (%)	34 (72.3)	17 (63.0)	17 (85.0)	0.095
Body mass index, kg/m^2	27.9 ± 6.0	27.8 ± 5.3	27.9 ± 6.6	0.951
NYHA classification II-III, %	53.3	7/13; 53.8	1/2; 50	0.920
Age at total repair, years	8.5 ± 7.4	9.9 ± 8.9	6.6 ± 4.3	0.129
Transventricular approach	25 (53.2)	14/27	11/20 (55.0)	0.367
Number of cardiac surgeries	1.9 ± 0.7	2.3 ± 0.8	2.1 ± 0.97	0.380
Transannular patch, n, (%)	27 (57.4)	14/27	13/20	0.831
Biventricular pacing system (CRT-D), n, (%)	6 (12.8)	6 (22.2)	0 (0.0)	N/A
EPS, n, (%)	28 (59.6)	9 (33.3)	19 (95.0)	0.001
VT/VF induction, n, (%)	20/28 (71.4)	6/9 (66.7)	14/19 (73.7)	0.701
BNP, pg/mL	232.8 (92.5-420.7)	385.8 (103.8-855.0)	140.2 (51.5-226.2)	0.286
Creatinine, μmol/L	83.7 ± 25.0	87.5 ± 29.3	79.3 ± 18.4	0.295
QRS duration, ms	174.2 ± 29.3	175.8 ± 28.1	172.6 ± 31.2	0.742
Echocardiogram				
LV EF, %	49.8 ± 14.4	47.7 ± 16.3	52.2 ± 11.6	0.329
RV area Di, cm^2/m^2	25.3 ± 7.1	24.6 ± 6.7	25.8 ± 7.9	0.765
RV volume index, cc/m^2	178.0 ± 43.5	180.5 ± 21.4	177.2 ± 49.5	0.900
RV FAC, %	30.1 ± 7.8	36.4 ± 7.1	28.2 ± 7.3	0.066
RV systolic pressure, mm Hg	42.5 ± 13.7	41.6 ± 9.5	43.6 ± 17.6	0.670
MRI				
LV EF, %	49.0 ± 10.9	46.2 ± 12.0	51.3 ± 9.7	0.233
LV EDV, mL	199.8 ± 67.8	202.3 ± 59.9	197.5 ± 76.7	0.866
LV EDVI, mL/m^2	102.0 ± 36.4	106.6 ± 36.5	98.4 ± 37.1	0.571
RV EF, %	37.1 ± 7.3	38.9 ± 7.1	35.3 ± 7.2	0.171
RV EDV, mL	303.8 ± 106.9	252.8 ± 56.5	362.7 ± 122.3	0.004
RV EDVI, mL/m^2	168.5 ± 59.8	141.9 ± 33.2	193.4 ± 69.0	0.017
Late gadolinium enhancement, n, (%)	13/18 (72.2)	5/9 (55.5)	8/9 (88.9)	0.114
Presenting rhythm (VT), n, (%)	33 (70.2)	19 (70.3)	14 (70.0)	0.854
Presenting rhythm (VF arrest), n, (%)	14 (29.8)	8 (29.6)	6 (30.0)	
Heart failure admission history, n, (%)	8 (17.0)	5 (18.5)	3 (15.0)	0.751
Previous AT/AF, n, (%)	11 (23.4)	5 (18.5)	6 (30.0)	0.358
Coronary artery disease, n, (%)	2 (4.2)	2 (7.4)	0 (0.0)	N/A
β-Blocker, n, (%)	23 (48.9)	12 (44.4)	11 (55.0)	0.711
Bisoprolol n, mg	7,4.5 ± 2.9	3,5.8 ± 3.8	4,3.4 ± 1.9	0.316
Metoprolol n, mg	14,29.5 ± 17.4	8,34.4 ± 22.0	6,22.9 ± 5.1	0.237
Atenolol n, mg	1,12.5	N/A	1,12.5	N/A
Carvedilol n, mg	1,3.125	1,3.125	N/A	N/A
Amiodarone, n, (%)	18 (38.2)	9 (33.3)	9 (45.0)	0.697
Amiodarone, mg	216.7 ± 92.4	211.1 ± 109.3	222.2 ± 78.2	0.807

Data are presented as mean ± SD or n (%) except where otherwise noted.

AF, atrial fibrillation; AT, atrial tachycardia; BNP, brain natriuretic peptide; CRT-D, cardiac resynchronization therapy defibrillator; Di, diastolic index; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; EPS, electrophysiology testing; FAC, fractional area change; LV, left ventricular; MRI, magnetic resonance imaging; N/A, not applicable; NYHA, New York Heart Association; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

patients with biventricular pacing (38.1% vs 10.0%; $P = 0.036$). No patient with previous RFCA before device implantation received appropriate ICD shocks. Five patients in the noninvasive group (n = 27) underwent RFCA procedures after receiving the first appropriate ICD shock. No patient experienced a second appropriate ICD shock after the RFCA procedure during a median follow-up of 57.8 (IQR, 48.6-125.8) months. On the contrary, 1 patient in the noninvasive group who did not undergo RFCA after the first ICD shock, sustained a second appropriate ICD shock (Fig. 2). Logistic regression analysis showed that invasive therapy alone significantly reduces the risk of ICD shock by 81.1% (OR, 0.189; 95% CI, 0.036-0.990; $P = 0.049$; Table 2).

Inappropriate ICD shocks

In total, 6 patients (12.8%) in our cohort received an inappropriate shock during the follow-up period, with an annual incidence of 2.2% per year. Four patients received inappropriate shock because of atrial tachycardia and 1 patient because of atrial fibrillation. One patient received an inappropriate shock because of lead fracture. A tendency toward less inappropriate shock was noted with invasive therapy (18.5% vs 5.0%; $P = 0.170$). The details of all ICD therapies are shown in Supplemental Table S3.

Composite outcomes

In total, 17 (36.2%) patients developed composite outcomes. A patient with ICD shock died because of a noncardiac cause (small cell carcinoma) and 1 patient underwent heart transplantation because of progressive heart failure. Among 8 patients who received ICD shock, hospitalization because of heart failure was reported in 7 patients (3 of them were hospitalized after ICD shock). There was a significant

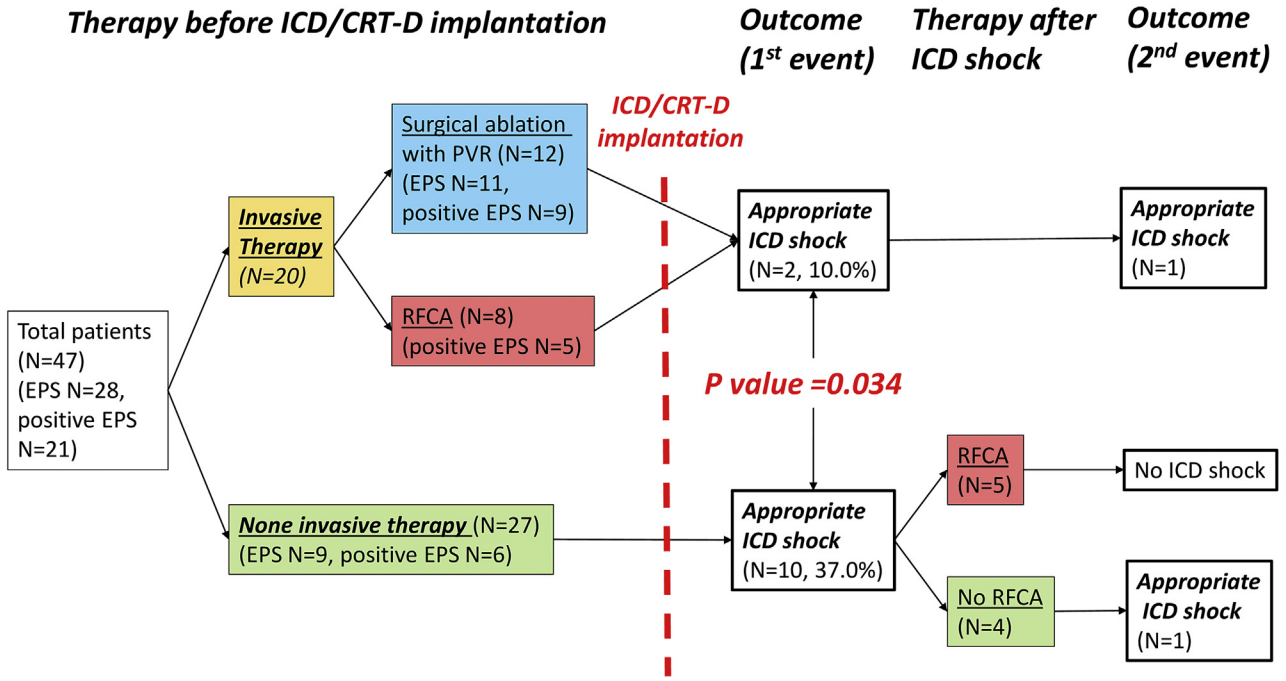

Figure 2. Clinical course before and after device implantation. CRT-D, cardiac resynchronization therapy defibrillator; EPS, electrophysiology testing; ICD, implantable cardioverter defibrillator; PVR, pulmonary valve replacement; RFCA, radiofrequency catheter ablation.

Table 2. Predictors of ICD shock

	OR	95% CI	*P*
Male sex	1.200	0.268-5.369	0.812
BMI	0.995	0.871-1.136	0.940
Age at total repair	0.966	0.906-1.030	0.287
Invasive vs noninvasive therapy	0.189	0.036-0.990	0.049
Multiple vs single surgery (not including PVR)	1.731	0.317-9.445	0.526
TA patch	1.500	0.401-5.605	0.547
Transventricular vs transannular approach	1.322	0.351-4.976	0.680
QRS duration $\geq$ 180 ms	1.545	0.361-6.610	0.557
LV EDP (obtained using catheter), mm Hg	0.967	0.789-1.184	0.744
Echocardiography			
LV EF, %	0.968	0.916-1.023	0.252
RV FAC (%)	1.023	0.864-1.212	0.788
RV area Di, cm^2/m^2	1.008	0.809-1.255	0.944
RV volume index, cc/m^2	0.995	0.963-1.029	0.775
RV systolic pressure > 60 mm Hg	1.636	0.160-16.73	0.678
MRI			
LV EF, %	0.978	0.882-1.085	0.678
LV EDV, mL	1.007	0.988-1.026	0.454
LV EDVI, mL/m^2	1.016	0.978-1.056	0.418
RV EF, %	1.028	0.916-1.154	0.638
RV EDV, mL	1.004	0.995-1.014	0.392
RV EDVI, mL/m^2	1.003	0.986-1.021	0.698
Late gadolinium enhancement	3.667	0.354-38.03	0.276
Heart failure admission history	3.875	0.791-18.98	0.095
Previous AT/AF, %	1.125	0.244-5.177	0.880
Amiodarone	0.356	0.081-1.569	0.172
β-Blocker	0.765	0.200-2.927	0.695

AF, atrial fibrillation; AT, atrial tachycardia; BMI, body mass index; CI, confidence interval; Di, diastlic index; EDP, end-diastolic pressure; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; FAC, fractional area change; ICD, implantable cardioverter defibrillator; LV, left ventricular; MRI, magnetic resonance imaging; OR, odds ratio; PVR, pulmonary valve replacement; RV, right ventricular; TA, tricuspid annulus.

difference in composite outcomes between the invasive group and the noninvasive group (OR, 0.090; 95% CI, 0.025-0.365; $P = 0.013$).

Discussion

Our retrospective study showed that invasive modification of the right ventricular substrate before ICD implantation was safe and associated with a lower likelihood of ICD shocks in the post repaired TOF patients. Invasive therapy was also associated with a reduction in the risk of composite outcomes of ICD shock, death, cardiac transplantation, and hospital admission compared with the noninvasive group.

Substrate modification and occurrence of ICD shock

An invasive strategy attempting modification of the right ventricular substrate was associated with a lower likelihood of defibrillator shocks in our study (10.0% vs 37.0%; $P = 0.036$). Four potential slow-conducting VT isthmuses have been identified around RVOT patch/scar and VSD scar/patch and transection of these anatomic isthmuses by RFCA was shown to abolish clinical VT on long-term follow-up,[13,14,22] Although identification of channels of activation using entrainment/resetting criteria during VA seems to be ideal, hemodynamic instability due to fast VT rate[7,14] often limits activation mapping in this group of patients. Prophylactic substrate-based RFCA is safe and has also been shown to reduce the incidence of ICD therapy for the secondary prevention of SCD in patients with ischemic cardiomyopathy.[12]

Twelve (25.5%) patients underwent SA with PVR. RV dilatation from volume overload of pulmonary regurgitation or pressure overload of pulmonary stenosis is an indicator of increased circuit length and might contribute significantly to

VT substrate formation. PVR alone does not reliably protect against VA and SCD,[19] indicating the additional role of critical areas of slow conduction in pathogenesis. A combination of reduction of hemodynamic stress by PVR and modification of critical isthmuses by intraoperative cryoablation (surgical ablation) can lead to a significant reduction in the incidence of monomorphic VT.[20] SA is reported to be safe and effective to prevent VA[23] in patients who require surgical PVR.[14,24] In our cohort of surgical ablation, 33.3% of patients received empiric ablation of AI 3 (1 with AI 4 as well) without any substrate mapping (preoperative or intraoperative). Although intraoperative mapping is described as a tool for mapping the AI(s) for patients who are not eligible for preoperative EPS, empiric intraoperative cryoablation involving AI 3 is reported to be safe and effective in the prevention of VA.[18]

Occurrence of defibrillator shocks in repaired TOF

In the present study, 25.5% (n = 12) suffered appropriate ICD shocks during follow-up. The incidence of appropriate ICD therapy has been reported to be between 19.0% and 30.6% over a follow-up period of 2.2-3.7 years in other studies.[7,25,26] Reports focused on ICD shocks in secondary prevention are limited. Khairy et al. reported that the annual rate of appropriate ICD shocks was 9.8% in TOF patients with secondary prevention ICDs.[7] In our study, the annual incidence of appropriate ICD shock was lower (4.6% per year) than in previous studies. The incidence of appropriate ICD shock in the invasive therapy group was relatively low (2.3% per year), which might contribute to an overall reduction of appropriate ICD shock in our population. Besides, different patient demographic characteristics such as relatively older age (43.1 ± 13.2 years old) at device implantation and high prevalence of CRT-D (n = 6; 12.8%) might influence ICD events.

We showed that invasive therapy alone was associated with the risk reduction of recurrent ICD shocks (OR, 0.189; $P = 0.049$). Clinical features, electrocardiogram, catheterization, and imaging parameters have been described as predictors of VA risk in patients with TOF. However, all of these parameters were described in the context of primary prevention. Khairy et al. described the role of elevated LV end-diastolic pressure and nonsustained VT as a predictor of ICD shock only in primary prevention.[7] It is likely that the patients who fulfil the criteria for secondary prevention are already at high risk and classical criteria do not offer any additional advantage for further risk stratification.

Substrate modification and inappropriate ICD shock

Six (12.8%) patients in our study received an inappropriate shock, which is lower than the description of almost 25% described by Khairy et al.[7] This difference can not be explained only by the use of amiodarone. Most of the inappropriate ICD shocks resulted from atrial tachycardia/flutter. RV volume overload and higher RV systolic pressure have been reported to predispose to right atrial (RA) tachycardia.[7,27] Pulmonary regurgitation and pulmonary stenoses are common causes of RV volume and pressure overload, respectively. Twelve patients (25.5%) in our cohort underwent PVR and 3 patients (6.4%) underwent CTI ablation or RA maze. Indirect or direct modifications of the RA substrate in more than a quarter of patients might have contributed to a relatively low incidence of inappropriate shock in our group.

Composite outcomes after invasive therapy

Our study showed that invasive therapy was associated with a reduction of composite outcomes ($P = 0.013$). The development of VA is often an indicator of progressive hemodynamic change.[28] Therefore, intervention for residual hemodynamic or structural defects should be addressed as part of arrhythmia control. However, some patients with VA might develop lethal arrhythmia without residual structural defects. These patients might benefit from catheter ablation per se.

Limitations

First, this study was a nonrandomized retrospective analysis of a relatively small number of participants from a single centre. Data were acquired retrospectively, and the number, interval, and documentation of clinical visits varied between patients. Discrepancies were noted in the usage of amiodarone, β-blockers, the prevalence of coronary artery disease, and the incidence of late gadolinium enhancement, among the invasive and the noninvasive group (Table 1). Although the difference in these parameters did not achieve statistical significance, possibly because of the small sample size, these factors might affect the calculated measures of association. Another limitation of the study is the lack of standardized screening protocols for rhythm monitoring and ICD programming, and the paucity of data on management details like antiarrhythmic drugs and combination of the strategies of RFCA and cryoablation. Second, the programming of ICD therapy has also changed, and device technology has evolved over the past years. ICD programming was also not standardized across all patients. Third, nonrandom selection of patients for the therapeutic strategy (invasive vs noninvasive) could affect outcomes as a result of indication bias. Fourth, in a significant number of patients in the "invasive" group, 2 interventions (PVR and RFCA) were performed. It is unclear which of these was the actual beneficial procedure. The fact that a small number of patients who underwent RFCA also showed benefit seems to suggest that it is the ablation part that reduced future incidence of VA, but this is far from proven. Finally, we performed an aggressive VT stimulation protocol with up to 5 extra stimuli, which might result in more of clinical VAs as well as nonclinical arrhythmias. The significance of this protocol is a matter of ongoing work.

Conclusion

Prophylactic substrate-based ablation is safe and associated with a lower likelihood of ICD shocks in the TOF population. However, retrospective data from this single-centre, small cohort is hypothesis-generating and future large, multicentre studies will be required to test the hypothesis.

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Disclosures

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Supplementary Material

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