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JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 10, NO. 12, 2024

ORIGINAL RESEARCH

VENTRICULAR ARRHYTHMIAS

Ventricular Tachycardia Substrates in Children and Young Adults With Repaired Tetralogy of Fallot

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ABSTRACT

BACKGROUND Patients with repaired tetralogy of Fallot (rTOF) have a time-dependent increased risk of ventricular tachycardia (VT). Slow conducting anatomical isthmuses (SCAIs) are the dominant VT substrates in adults with rTOF. It is unknown if they are present at younger age.

OBJECTIVES This study aimed to characterize VT substrates in patients with rTOF <30 years of age.

METHODS Data of consecutive patients with rTOF aged <30 years who underwent electroanatomical mapping and programmed electrical stimulation between 2005 and 2022 were analyzed.

RESULTS Fifty-five patients were included (median age: 15.8 years, IQR: 13.8-21.8 years; 15 repaired via ventriculotomy; 13 complex TOF variants). Twelve patients had right ventricle-to-pulmonary artery conduits inserted during initial repair or had early pulmonary valve replacement (PVR) (<1 year after repair). Indications for electroanatomical mapping and programmed electrical stimulation were spontaneous VT, before PVR, and risk stratification in 5, 40, and 10 patients, respectively. In 16 patients (29%), SCAI 3 was identified; no other SCAI was present. Monomorphic VT was inducible in 8 and related to SCAI 3 in 7 patients. Identified VT substrates were targeted by ablation. Right ventricle-to-pulmonary artery conduit/early PVR, ventriculotomy, and complex TOF were associated with SCAI 3 in univariable analysis. During a median follow-up of 5.3 years, VT recurred in 2 patients. No patients died.

CONCLUSIONS In young patients with rTOF, SCAI 3 is the dominant substrate for VT. Complex TOF and interrelated type and timing of (re-)operation may contribute to the development of SCAI 3 already at a young age.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 26, 2023; revised manuscript received July 17, 2024, accepted July 31, 2024.

ISSN 2405-500X https://doi.org/10.1016/j.jacep.2024.07.016

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 10, NO. 12, 2024
DECEMBER 2024:2613–2624

ABBREVIATIONS AND ACRONYMS

CL = cycle length

DORV = double outlet right ventricle*

EAM = electroanatomical mapping

EPE = electrophysiological evaluation*

ICD = implantable cardioverter-defibrillator

MSVT = monomorphic sustained ventricular tachycardia*

PA = pulmonary artery

PES = programmed electrical stimulation*

PVR = pulmonary valve replacement*

RFCA = radiofrequency catheter ablation

(r)TOF = (repaired) tetralogy of Fallot

RV(OT) = right ventricle (outflow tract)

RV = right ventricular

(SC)AI = (slow conducting) anatomical isthmus

VA = ventricular arrhythmia

VSD = ventricular septal defect

VT = ventricular tachycardia

The prevalence of patients with repaired tetralogy of Fallot (rTOF) and its morphological spectrum is increasing as improved medical and surgical care lead to better survival into late adulthood.[1,2] Despite early surgical repair patients remain at risk for late ventricular tachycardia (VT) and sudden cardiac death.[3,4] The propensity for VT and sudden cardiac death increases from the age of 30 years and more steeply after the age of 45 years.[3,5-10] As a consequence, patients with rTOF referred for radiofrequency catheter ablation (RFCA) of VT are typically middle-aged adults.[6,9-12] Electroanatomical mapping (EAM) studies could demonstrate that slow conducting anatomical isthmuses (SCAI), bordered by unexcitable tissue such as valve annuli, patch material, and ventricular incisions, are the dominant VT substrate in adult patients with rTOF.[6,13] The most prevalent SCAI is SCAI 3, located between the pulmonary annulus and the ventricular septal defect (VSD) patch.[6] It has been speculated that chronic pressure and/or volume overload together with aging may lead to adverse remodeling, progressive fibrosis, and slow conduction over time.[14] Data on VT and related substrates in young patients with rTOF are scarce. Whether a SCAI as a potential VT substrate is already present at young age is unknown.

A high proportion of patients with rTOF will undergo surgical or percutaneous pulmonary valve replacement (PVR) later in life.[15] Because of the potential inaccessibility of SCAI after PVR, EAM and programmed electrical stimulation (PES) has been implemented since 2007 in our routine work-up of all patients with rTOF ≥8 years before PVR.[16]

The aims of this study were to evaluate the prevalence of SCAI in patients with rTOF <30 years of age, to determine the substrate of spontaneous and induced VT, and to identify factors associated with SCAI in this age group.

METHODS

STUDY SAMPLE. The study sample consisted of all consecutive patients with rTOF and related lesions younger than 30 years at time of electrophysiological evaluation (EPE) at the Leiden University Medical Centre between 2005 and 2022. Eligible for inclusion were patients with classical TOF, TOF with double outlet right ventricle (DORV), TOF or DORV with absent pulmonary valve, and pulmonary atresia with VSD.[17,18] All morphologies except classical TOF and TOF with DORV were classified as complex TOF variants. Patients provided informed consent before the procedure.

The indications for EPE, including EAM and PES, were: 1) spontaneous ventricular arrhythmia (VA); 2) evaluation before PVR; and 3) risk stratification for VA, based on a combination of risk factors according to our institutional protocol.[6,13,19] Clinical characteristics and the details of prior surgeries and percutaneous interventions were extracted from the medical records. The 12-lead electrocardiogram, transthoracic echocardiography, and cardiac magnetic resonance images were reviewed.

Surgical repair was categorized as ventriculotomy if repair was performed through a right ventricular incision or as transatrial-transpulmonary, which included minor extension of a transpulmonary incision into the right ventricular outflow tract (RVOT). PVR or right ventricle (RV) to pulmonary artery (PA) conduit insertion was defined as early if performed *during* initial intracardiac repair or *within the first year* after intracardiac repair.

This study was approved by the internal review board of the cardiology and pediatric cardiology department. The Medical Ethics Committee Leiden The Hague Delft waived the need for written informed consent (GP21.137).

EPE. Three-dimensional EAM and PES were performed under conscious sedation or general anesthesia, depending on patient characteristics. PES protocol included up to 4 drive-cycle lengths (CLs) from the RV apex and the RVOT close to the anatomical isthmus (AI) with up to 4 extra stimuli down to refractory period or 180 ms and, if VT was not inducible, isoproterenol infusion. Inducibility for monomorphic sustained VT (MSVT) was defined as monomorphic VT lasting for ≥30 seconds or requiring termination because of hemodynamic compromise. High-density voltage and activation mapping were performed during sinus rhythm using the Thermo-Cool catheter and the CARTO system (Biosense Webster Inc). At sites with a bipolar voltage of <1.5 mV, high output pacing was performed to identify unexcitable tissue as boundaries for the previously described AIs, namely: AI 1 bordered by transannular/RVOT patch/RV incision and tricuspid annulus, AI 2 by nontransannular RVOT patch/RV incision and pulmonary annulus, AI 3 by VSD patch and pulmonary annulus, and AI 4 by VSD patch and tricuspid annulus.

At the entrance and exit sites of an AI, the local activation time was determined and the conduction time and conduction velocity were calculated as previously described.[6] In case of a narrow QRS or colliding wavefronts within an AI, pacing at the AI entrance was performed and the conduction velocity calculated. A SCAI was defined as a conduction velocity of <0.5 m/s across the AI.

In case of SCAI, RFCA using irrigated tip catheters or intraoperative surgical cryoablation[16] was performed to transect the SCAI by connecting the unexcitable boundaries. Endpoints of a successful ablation were bidirectional block across the ablation line (RFCA and cryoablation) and noninducibility of VT (RFCA). Surgical cryoablation was performed on a beating heart, allowing the assessment of bidirectional block using differential pacing techniques in the operating room.[16]

Patients were followed for VT recurrence and mortality.

DATA ANALYSIS. Categorical data were displayed as frequencies with percentages and compared with the Fisher's exact or chi-squared test. Continuous data were reported as mean ± SD or median with interquartile range (25th and 75th percentiles) or range, and were compared using the *t*-test or Mann-Whitney *U* test. To evaluate a potential association between clinical and surgical parameters and SCAI, univariable logistic regression analysis was performed and odds ratios (ORs) with 95% CIs were reported, if statistically significant. Variables related to the surgical intervention included RV-PA conduit during repair/early PVR (<1 year after repair), ventriculotomy, and late PVR (>1 year after repair). The small sample size and prevalence of SCAI do not allow for a multivariable logistic regression analysis, which was not performed. Follow-up time was calculated with the reverse Kaplan-Meier method. Statistical analyses were performed using SPSS 25.0 (IBM Corp). Statistical significance was defined as a *P* value of <0.05.

RESULTS

PATIENT CHARACTERISTICS. Of 146 consecutive patients with rTOF who underwent EAM, 55 patients (55% male) were <30 years of age and comprised the study cohort. The median age at EPE was 15.8 years (IQR: 13.8-21.8 years). The indications were spontaneous VA in 5 (9%), before (re)PVR in 40 (73%), and risk stratification in 10 patients (18%). Of the 5 patients with spontaneous VA (median age: 21.3 years; range: 11.3-24.4 years), 4 had a documented MSVT (median VT cycle length [CL]: 230 ms; range: 200-248 ms) and 1 had VF, as first documented arrhythmia (Figure 1).

Thirty-three patients (60%) had classical TOF, 9 (16%) TOF with DORV, and 13 (24%) had complex TOF variants, of whom 8 had pulmonary atresia-VSD and 2 an absent pulmonary valve (Table 1). The median age at repair was 9.6 months (IQR: 4.7-17.2 months) and 16 (29%) had a prior palliative shunt. In 15 patients (27%), a ventriculotomy was performed and in 45 (82%) a transannular/RVOT patch was inserted.

Twelve patients (22%) had either an RV-PA conduit implantation during initial repair (n = 10) at a median age of 0.7 years (IQR: 0.3-1.2 years) or had early PVR (n = 2) (patient ages 0.4 and 5.0 years). Reasons for early PVR were pulmonary valve endocarditis in the first and prevention of pulmonary regurgitation after redo infundibular resection in the second. Two patients with RV-PA conduit insertion during repair required early redo PVR (<1 year after repair). In 14 patients (25%), PVR was performed late, at a median age of 10.1 years (IQR: 2.7-14.3 years), of whom in 8 patients PVR was performed in a native RVOT (age at late PVR 10.6 years; IQR: 7.5-14.6 years) and 6 had an initial RV-PA conduit/early PVR (age at late PVR 2.9 years; IQR: 2.2-11.5 years) (Figure 2).

PREPROCEDURAL EVALUATION. The mean QRS duration was 142 ± 29 ms. All patients had normal or mildly reduced systolic left ventricular function corresponding to a mean ejection fraction of 55% ± 29% on cardiac magnetic resonance. Only 2 patients (4%) had moderate to severe systolic RV dysfunction. Indexed RV end-diastolic and -systolic volume on cardiac magnetic resonance were 129 mL/m^2 (IQR: 101-169 mL/m^2) and 67 mL/m^2 (IQR: 48-89 mL/m^2), respectively, and the mean RV ejection fraction was 49% ± 7%.

EPE. All but 1 patient were in sinus rhythm. AI 1 and AI 3 could be identified in all; 1 had AI 4, and none AI 2. AI 3 showed slow conduction in 16 (29%) and was blocked in 2. No other AI demonstrated slow conduction properties. Four of 5 patients (80%) with spontaneous VA had a SCAI 3. The other patient had a basal inferolateral RV scar as VT substrate. Among patients in whom EPE was performed before PVR, 11 of 40 (28%), and among patients evaluated for risk stratification, 1 of 10 (10%), had SCAI 3.

A total of 9 MSVT (mean VTCL 238 ± 29) were inducible in 8 patients (15%), which were proven related to SCAI 3 in 7 of 8 patients (88%) (Figure 3). Hence, 7 of 16 (44%) patients with SCAI 3 were inducible for VT. Of note, patients with SCAI 3 and VT inducibility had a median age of 21.7 years (IQR: 14.7-24.4 years) at the time of EPE, in comparison with a

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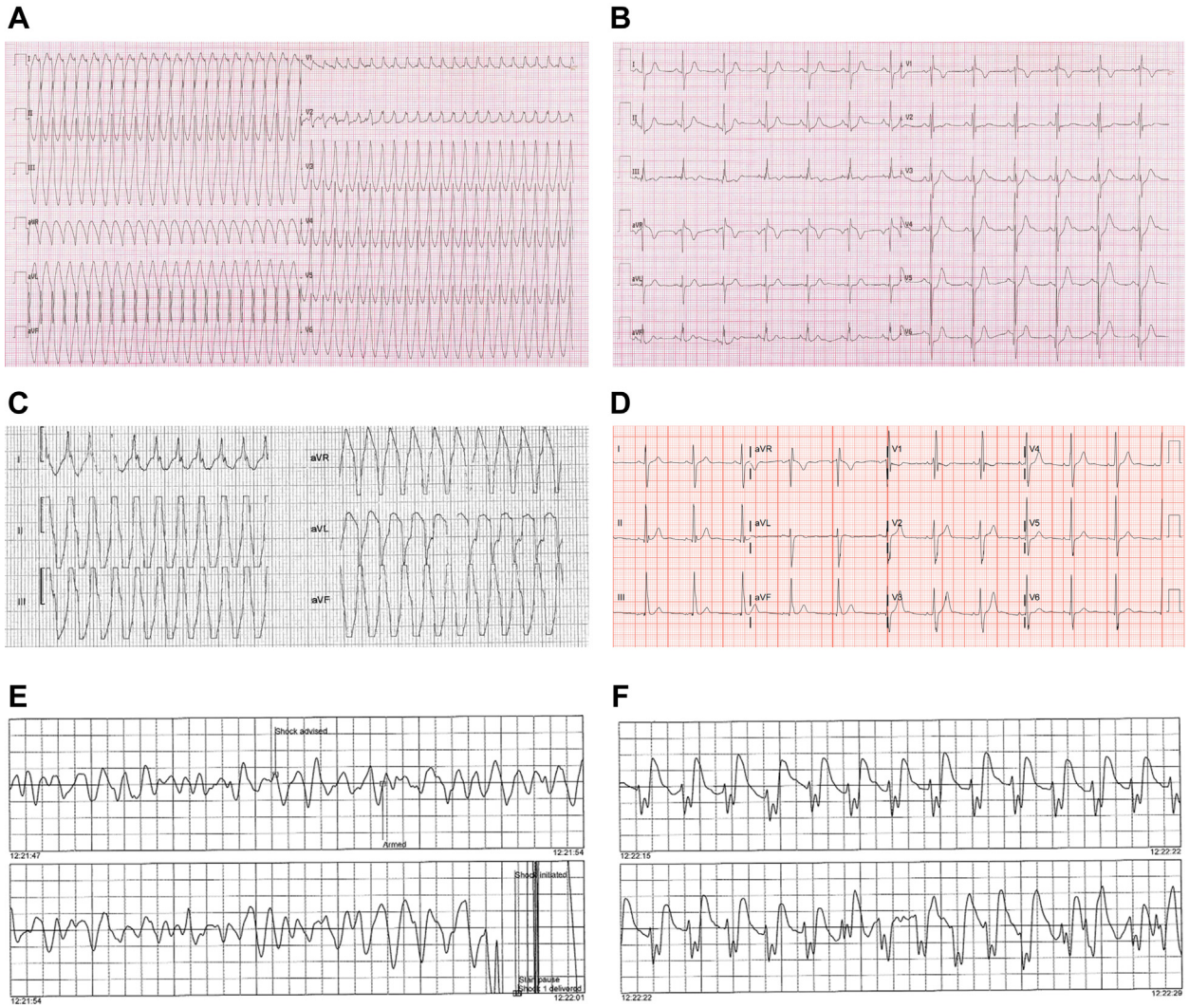
FIGURE 1 **Fast VTs in Young Patients With rTOF**



(A) A patient with rTOF, aged 11 years, presented with hemodynamically unstable VT (CL 226 ms, RBBB configuration). Amiodarone and adenosine were without effect. The patient was converted to SR with electrical cardioversion. The SR ECG (B) showed a QRS complex width of 102 ms with incomplete RBBB. SCAI 3 was confirmed as VT substrate. (C) A 21-year-old patient with rTOF who presented with hemodynamically tolerated VT (CL 248 ms, LBBB configuration). After spontaneous conversion, the SR ECG (D) showed incomplete RBBB. SCAI 3 was targeted for ablation. (E) A 14-year-old patient with pulmonary atresia-VSD and RV-PA conduit during repair presented with out-of-hospital cardiac arrest with ventricular fibrillation. The rhythm strokes illustrate return of spontaneous circulation after shock (F). At electrophysiological evaluation, a VT with CL 272 ms was induced, which was related to SCAI 3. CL = cycle length; EAM = electroanatomical mapping; ECG = electrocardiogram; SR = sinus rhythm; PVR = pulmonary valve replacement; RBBB/LBBB = right/left bundle branch block; rTOF = repaired tetralogy of Fallot; RV-PA = right ventricle-to-pulmonary artery; SCAI 3 = slow conducting anatomical isthmus 3; VSD = ventricular septal defect; VT = ventricular tachycardia.

median age of 14.3 years (IQR: 12.0-16.6 years) in noninducible patients with SCAI 3 ($P = 0.071$). With completion of the induction protocol polymorphic VT or VF could be induced in 3 and 5 patients (1/3 and 3/5 with SCAI 3), respectively. One patient required dobutamine administration during mapping and one patient had a conservatively managed arteriovenous fistula. There were no serious adverse events.

CLINICAL PARAMETERS RELATED TO SCAI. Clinical, surgical, electrocardiogram and imaging characteristics are provided in Table 1. SCAI 3 was more often observed among patients with complex TOF variants (8/13 [62%]), who were repaired via ventriculotomy (9/15 [60%]), and who underwent initial repair with an RV-PA conduit or required early PVR (9/12 [75%]) (Central Illustration, Figure 4). In contrast, only 5 of 35

TABLE 1 Baseline Characteristics

	All (N = 55)	SCAI 3− (n = 39)	SCAI 3+ (n = 16)	*P* Value
Male, %	30 (55)	19 (49)	11 (69)	0.175
Age at procedure, y	15.8 (13.8-21.8)	16.0 (14.1-21.8)	15.8 (12.4-22.8)	0.725
Body mass index (kg/m^2)	20.9 ± 4.1	21.2 ± 4.3	20.6 ± 3.6	0.629
Morphology				
Classical TOF	33 (60)	27 (69)	6 (38)	0.029
TOF with DORV	9 (16)	7 (18)	2 (13)	>0.999
Complex TOF variants				
All	13 (24)	5 (13)	8 (50)	0.003
Pulmonary atresia-VSD	8 (15)	3 (8)	5 (31)	-
Pulmonary atresia-VSD with MAPCAs	4 (7)	-	4 (25)	-
Pulmonary atresia-VSD without MAPCAs	4 (7)	3 (8)	1 (6)	-
TOF/DORV with absent pulmonary valve	2 (4)	-	2 (13)	-
Other complex TOF[a]	3 (5)	2 (5)	1 (6)	-
Lesion characteristics				
VSD classification				
Outlet VSD	41 (98)	31 (97)	10 (100)	>0.999
Inlet VSD	1 (2)	1 (3)	-	
PFO or ASD	31 (61)	22 (59)	9 (64)	0.753
Patent ductus arteriosus	10 (20)	8 (22)	2 (14)	0.707
Bicuspid pulmonary valve	24 (47)	19 (51)	5 (36)	0.318
Severe cyanosis or cyanotic spells before repair	18 (46)	14 (45)	4 (50)	>0.999
Genetic condition	6 (11)	5 (13)	1 (6)	0.660
Surgical history				
Palliative shunt[b]	16 (29)	12 (31)	4 (25)	0.754
Age at initial repair, mo	9.6 (4.7-17.2)	9.6 (4.7-14.2)	9.9 (5.2-24.2)	0.476
Ventriculotomy	15 (27)	6 (15)	9 (56)	0.002
Extensive infundibular resection	13 (27)	10 (28)	3 (25)	>0.999
Transannular patch[c]	42 (76)	35 (90)	7 (44)	0.421
RVOT patch	3 (5)	1 (3)	2 (13)	0.200
PVR				
Any PVR performed[d]	20 (36)	10 (26)	10 (63)	0.010
Age at first PVR, years[d]	2.4 (0.6-10.2)	8.3 (0.6-14.3)	0.9 (0.6-5.2)	0.190
Time between initial repair and first PVR, y[d]	0.0 (0.0-9.5)	7.0 (0.0-13.3)	0.0 (0.0-0.0)	0.023
RV-PA conduit during repair or PVR <1 y after repair	12 (22)	3 (8)	9 (56)	<0.001
PVR >1 y after repair	14 (25)	8 (21)	6 (38)	0.189
Additional surgery for RVOT obstruction	5 (9)	4 (10)	1 (6)	>0.999
Total number of intracardiac surgeries	2 (1-2)	2 (1-2)	2 (1-2.75)	0.520
Clinical history				
Pulmonary valve endocarditis	4 (7)	1 (3)	3 (19)	0.069
Percutaneous PV/PA dilatation or stenting				
No. of patients	8 (15)	4 (10)	4 (25)	0.212
No. of procedures per patient (if performed)[e]	2 (1-5)	1.5 (1-3)	3.5 (1-5)	0.343

Continued on the next page

patients (14%) with noncomplex TOF, without an RV-PA conduit during repair/early PVR, who underwent transatrial-transpulmonary correction, had a SCAI 3. No differences were found between patients with or without SCAI in materials used for intracardiac surgery or percutaneous intervention (Supplemental Table 1).

In univariable logistic regression RV-PA conduit during initial repair/early PVR (OR: 15.4; 95% CI: 3.3-71.8; $P < 0.001$), ventriculotomy (OR: 7.1; 95% CI: 1.9-26.4; $P = 0.004$), and complex TOF (OR: 6.8; 95% CI: 1.8-26.4; $P = 0.006$) seemed to be associated with SCAI 3 (**Table 2**). Late PVR (>1 year after repair) was not associated with SCAI 3 (OR: 2.3; 95% CI: 0.6-8.3; $P = 0.195$). Among patients who underwent EPE before PVR, initial RV-PA conduit insertion/early PVR (OR: 16.2; 95% CI: 2.5-104.4; $P = 0.003$), ventriculotomy (OR: 5.8, 95% 1.2-26.6; $P = 0.025$), and

TABLE 1 Continued

	All (N = 55)	SCAI 3– (n = 39)	SCAI 3+ (n = 16)	*P* Value
Clinical characteristics				
Electrocardiogram				
QRS duration, ms	142 ± 29	140 ± 28	148 ± 32	0.365
QRS duration ≥150 ms	27 (49)	18 (46)	9 (56)	0.496
QRS duration ≥180 ms	6 (11)	3 (8)	3 (19)	0.342
Cardiac magnetic resonance				
LVEF, %	55 ± 29	54 ± 7	56 ± 5	0.278
RVEF, %	49 ± 7	48 ± 7	49 ± 7	0.759
RVEDV/BSA, mL/m^2[f]	129 (101-169)	147 (104-179)	114 (90-162)	0.205
RVESV/BSA, mL/m^2[f]	67 (48-89)	76 (49-90)	61 (39-75)	0.334
Echocardiography				
Moderate/severe systolic LV dysfunction	-	-	-	-
Moderate/severe systolic RV dysfunction	2 (4)	2 (5)	-	>0.999
Medication				
Class I anti-arrhythmic drugs	-	-	-	-
Beta-blocker	3 (5)	2 (5)	1 (6)	>0.999
Class III anti-arrhythmic drugs	-	-	-	-
Verapamil/diltiazem	1 (2)	1 (3)	-	>0.999
ICD	1 (2)	-	1 (6)	0.291

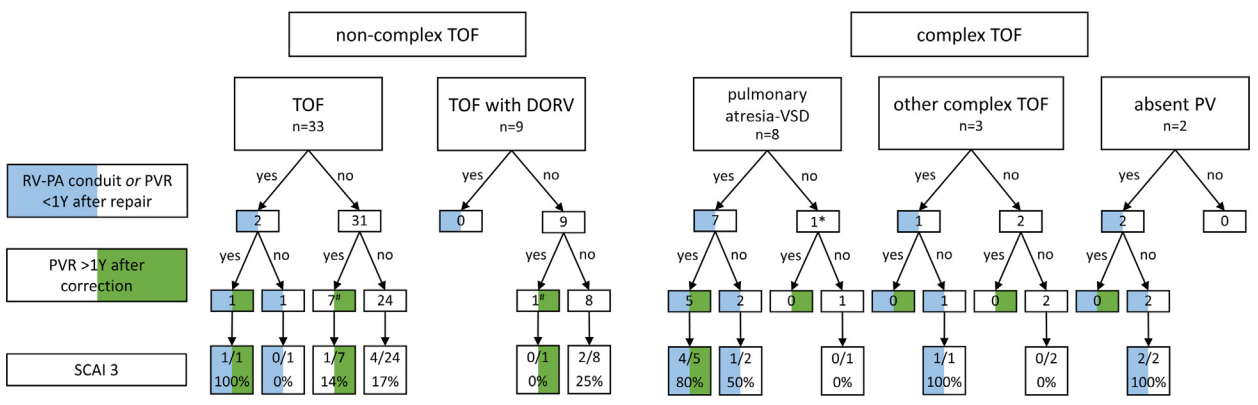
Values are n (%), median (Q1-Q3), or mean ± SD. Data on echocardiography was available in all and cardiac magnetic resonance data were available in 44 patients (80%). [a]Includes 2 with TOF/DORV with atresia of the left PA and MAPCAs and 1 with complex TOF with DORV. [b]Thirteen modified Blalock-Taussig shunts and 3 central shunts. [c]Analysis performed in patients without RV-PA conduit inserted during initial repair/early PVR. [d]Includes RV-PA conduit inserted during initial repair. [e]Median and range. [f]The Mosteller method was used to calculate BSA.

ASD/VSD = atrial/ventricular septal defect; BSA = body surface area; DORV = double outlet right ventricle; ICD = implantable cardioverter-defibrillator; LVEF/RVEF = LV/RV ejection fraction; LV/RV = left/right ventricle; MAPCAs = major aortopulmonary collateral arteries; PA = pulmonary artery; PFO = patent foramen ovale; PV = pulmonary valve; PVR = pulmonary valve replacement; RVEDV/RVESV = right ventricular end-diastolic/-systolic volume; RVOT = right ventricular outflow tract; RV-PA = right ventricle-to-pulmonary artery; SCAI 3 = slow conducting anatomical isthmus 3; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

complex TOF (OR: 5.8; 95% CI: 1.2-26.6; $P = 0.025$) remained associated.

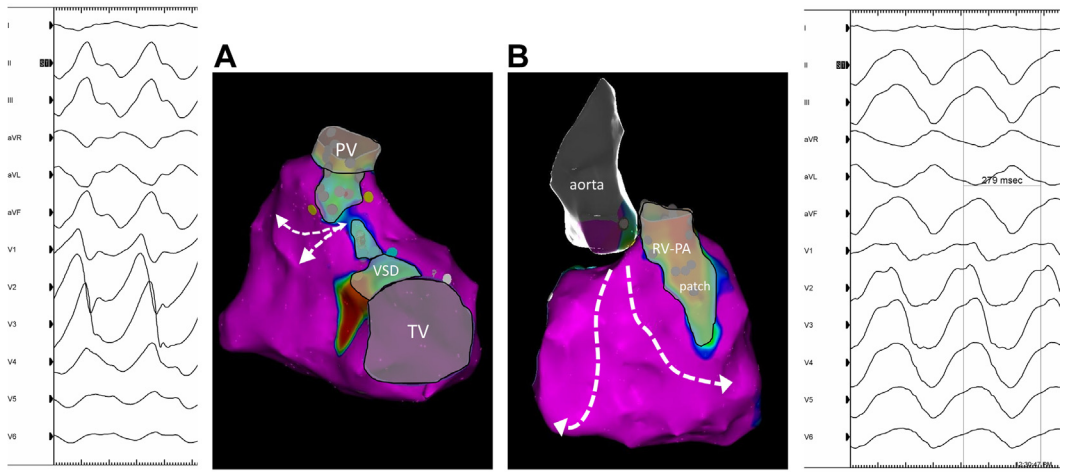
ABLATION OUTCOMES AND FOLLOW-UP. In patients who presented with spontaneous VA, the identified VT substrates were targeted by RFCA (n = 5). Two procedures were unsuccessful owing to an overlying PVR. In 4 patients (80%), an implantable cardioverter-defibrillator (ICD) was inserted. One

FIGURE 2 Flowchart of SCAI 3 Presence per Morphology, RV-PA Conduit/Early PVR, and Late PVR



*No RV-PA conduit insertion led to severe pulmonary regurgitation after repair with transannular patch. #One patient in each group received percutaneous PVR (Melody valve, Medtronic Inc) as a second PVR after prior homograft implantation. Neither had a SCAI 3. DORV = double outlet right ventricle; other abbreviations as in Figure 1.

FIGURE 3 **Induced VT in a Patient With an RV-PA Conduit**



An 18-year-old patient with pulmonary atresia with VSD repaired with an RV-PA conduit at 11 months. EAM demonstrated SCAI 3 with a conduction velocity of 0.4 m/s (not shown). Two monomorphic VTs were inducible which both used SCAI 3 as critical pathway for reentry. (A) Bipolar voltage map of the RV with a modified posterior view of AI 3 (between PV and VSD). Gray areas indicate unexcitable tissue. The induced VT1 was consistent with clockwise activation (as seen from anterior, white arrows indicate activation front) of AI 3 (left, RBBB pattern). (B) Bipolar voltage map as seen from modified anterior. Later, VT2 was induced (right, LBBB pattern) where the wavefront perpetuates through AI 3 in a counterclockwise manner. Ablation of SCAI 3 was not successful as artificial material overlying SCAI 3 prohibited durable lesion formation. TV = tricuspid valve; other abbreviations as in Figure 1.

patient who presented with a hemodynamically tolerated VT and had a successful ablation was discharged without an ICD.

In all patients who were evaluated before PVR and who had SCAI 3, surgical cryoablation was performed (n = 11), which was successful in 9 and probably successful in 2 (fast RVOT conduction prohibited differential pacing maneuvers). Postoperative EPE revealed persistent slow conduction through AI 3 in 1 patient. In this patient, RFCA failed to block SCAI 3 because the homograft covered SCAI 3, and the patient was discharged with an ICD.

Among patients who underwent EPE for risk stratification, 1 had SCAI 3, which could not be ablated successfully owing to prior surgical PVR. In this patient, an ICD was inserted.

There were no complications related to RFCA or surgical cryoablation.

After a median follow-up of 5.3 years (IQR: 2.8-8.2 years), VT recurred in 2 patients; both had prior spontaneous VT and ablation failure. No patient died.

DISCUSSION

To the best of our knowledge, this study is the first to evaluate the prevalence of SCAI, its relation to spontaneous and induced VT, and factors that may contribute to its development in young patients with rTOF. A SCAI 3 was present in 29% of patients with rTOF <30 years of age referred for EPE and was the dominant substrate for spontaneous and inducible VT in this age group. Despite a high prevalence of SCAI in these young patients, only 44% of patients with SCAI 3 were inducible for VT. Complex TOF variants, initial RV-PA conduit placement or early PVR within the first year after intracardiac repair, and ventriculotomy, may be associated with SCAI 3 in young rTOF.

SCAI IN YOUNG TOF PATIENTS. In prior series of middle-aged patients with rTOF who underwent EAM and PES for similar indications, the prevalence of SCAI was 31% to 38%.[6,12,20] SCAI 3 was observed most frequently (88% of the patients with any SCAI), followed by SCAI 1, 2, and 4.[20] The similar high

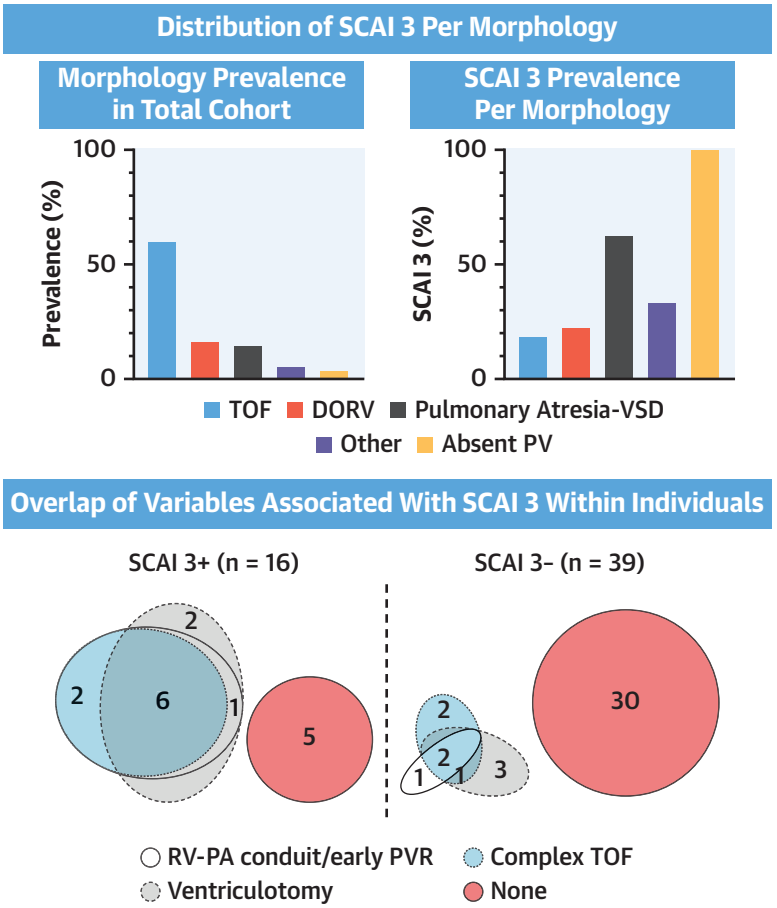
CENTRAL ILLUSTRATION **VT Substrates in Children and Young Adults With rTOF**

Patients (n = 55)
- Median age 15.8 years (IQR: 13.8-21.8 years)
- Median age at repair 9.6 months (IQR: 4.7-17.2 months)

Electrophysiological evaluation
- Before PVR in 73%
- SCAI 3 present in 29% (no other SCAI)
- Monomorphic sustained VT inducible in 44% of those with SCAI 3

Treatment
- All VT substrates targeted
- Radiofrequency catheter ablation in 6 patients
- Surgical cryoablation in 11 patients

Follow-up
- VT recurrence in 2 (4%) (follow-up 5.3 years)
- No mortality



Wallet J, et al. JACC Clin Electrophysiol. 2024;10(12):2613-2624.

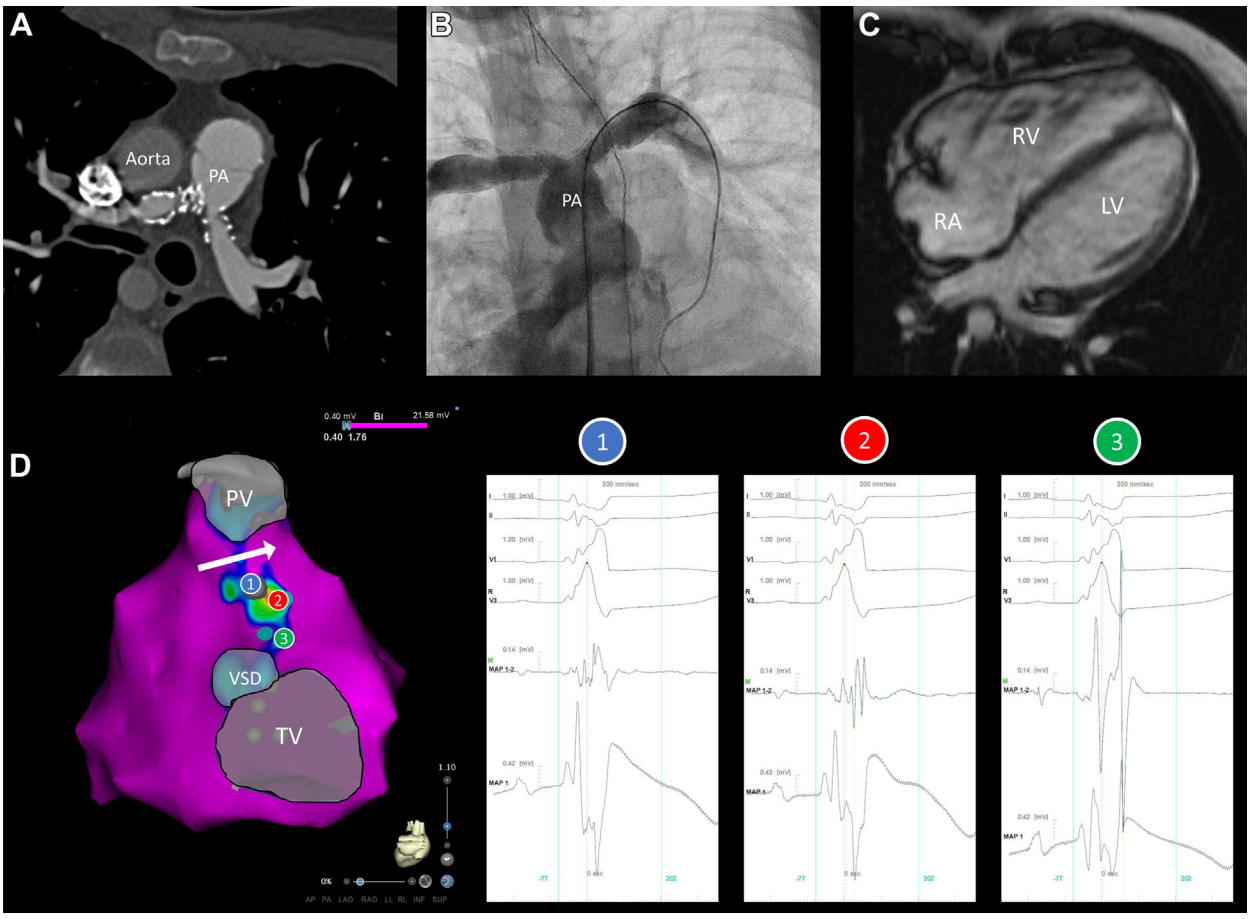
(Left) Main findings. (Top right) Distribution of SCAI 3 per morphology. (Bottom right) Euler diagrams illustrating the significant overlap of variables associated with SCAI 3 within patients with (+) and without (−) SCAI 3. The numbers in the ellipses represent the number of individuals with the variables in the legend. Plotted using R software, version 4.3.1, Eulerr package. DORV = double outlet right ventricle; IQR = interquartile range; PV = pulmonary valve; SCAI 3 = slow conducting anatomical isthmus 3; PVR = pulmonary valve replacement; RV-PA = right ventricle to pulmonary artery; TOF = tetralogy of Fallot; VSD = ventricular septal defect; VT = ventricular tachycardia.

prevalence of SCAI in the young patients with rTOF in our study is remarkable, considering a strong association between the time after initial repair and the presence of SCAI observed in older rTOF cohorts.[6] These data suggest that, in young patients with rTOF, additional factors apart from aging may contribute to slow conduction within an AI.

Despite the presence of AI 1 and 3 in all and AI 4 in 1, the only SCAI in our young cohort was SCAI 3. This finding can be explained partly by changing surgical access from transversal or longitudinal ventriculotomy to a transatrial-transpulmonary approach, systematically performed since the 1980s.[21] This approach excludes AI 2 and affects the characteristics of AI 1.[21] In addition, the currently preferred use of a smaller transannular patch results in a wider AI 1, which was found to be less likely arrhythmogenic.[6,21]

SPONTANEOUS AND INDUCIBLE VT. ICD interrogation studies have shown that the vast majority of VA in adult patients with rTOF are monomorphic and

FIGURE 4 SCAI 3 in a Patient With an RV-PA Conduit



A 15-year-old patient with pulmonary atresia with VSD and an RV-PA conduit at initial repair who in subsequent years required multiple percutaneous PA balloon dilatations and stents. (A) Computed tomography angiography of the main PA branching into right and left stenotic PAs. (B) Angiography with narrow origins of PA branches, prestenotic dilatation, and pulmonary regurgitation. (C) Cardiac magnetic resonance imaging indicated a dilated RV. The patient was listed for surgical PVR and PA angioplasty. (D) EAM of RV with bipolar voltages as seen from modified posterior with a low voltage area at AI 3. Near the tricuspid annulus double potentials were found, suggesting conduction block in this area (green dot, with corresponding bipolar [MAP 1-2] and unipolar [MAP 1] electrograms). More superiorly, electrograms showed fractionation (blue and red dots). Just below the PV, a pathway with slow conduction was present (white arrow). SCAI 3 was targeted with surgical cryoablation concomitant with PVR. Abbreviations as in Figure 1.

TABLE 2 Factors Associated With SCAI 3 in Univariable Analysis

	OR	95% CI	*P* Value
RV-PA conduit during repair or PVR <1 y after repair	15.4	3.3-71.8	<0.001
Ventriculotomy	7.1	1.9-26.4	0.004
Complex TOF	6.8	1.8-26.4	0.006

Considering the small sample size and prevalence of SCAI a multivariable logistic regression analysis was not performed.

Abbreviations as in Table 1.

typically fast VTs, with reported median VTCL between 282 and 290 ms.[22,23] In our young cohort, 4 of 5 patients with spontaneous VA had a documented MSVT with a median VTCL of 230 ms (range: 200-248 ms) and 1 patient presented with VF (Figure 1). It is likely that the latter may have had initially a fast MSVT degenerating to VF, supported by inducibility of a fast MSVT in this patient during PES.

In 8 patients with rTOF in our cohort, MSVTs could be induced, including all but 1 with spontaneous VA,

with SCAI 3 as critical substrate in 88%. The high prevalence of SCAI 3-dependent spontaneous and induced VTs has also been reported in adult rTOF cohorts.[6,20] However, despite the presence of SCAI 3, 9 of 16 young patients with rTOF (56%) were not inducible for a MSVT, compared with 7% non-inducible patients in older rTOF cohorts.[6] Induction of a macrore-entrant VT with SCAI as critical substrate requires unidirectional conduction block across the AI followed by recovery of conduction for the initiation of reentry VT. Rapid conduction in small sized right ventricles with potential collision of wavefronts at the AI may prevent unidirectional block in young rTOF. Indeed, patients who had SCAI 3 and were inducible for VT tended to be older at time of EPE in comparison with noninducible SCAI 3 patients (21.7 years [IQR: 14.7-24.4 years] vs 14.3 years [IQR: 12.0-16.6 years], respectively). Further studies are needed to investigate the cause of the lower VT inducibility despite the presence of SCAI, which may impact the value of PES without EAM for risk stratification at a young age.

FACTORS THAT MAY CONTRIBUTE TO EARLY DEVELOPMENT OF SCAI 3. In our young cohort, 56% of all patients with SCAI 3 had an RV-PA conduit implantation at initial repair or PVR within 1 year after repair. Patients with RV-PA conduits at initial repair may be more likely to require reoperation and therefore may be over-represented in our cohort; the main indication for EPE was assessment before PVR. However, in our series 22% of all patients had an RV-PA conduit, which is comparable with 14% to 21% RV-PA conduit patients in large series of patients with rTOF.[24,25]

In patients with rTOF, chronic pressure and/or volume overload, cyanosis, delayed repair, and aging have been associated with RVOT interstitial fibrosis and subsequent slow conduction over time.[14] Of note, no abnormal interstitial fibrosis was seen in those operated before the age of 2 years. Patients in our cohort underwent early repair at a median age of 9.6 months. Volume overload owing to PV regurgitation may be another causative factor contributing to abnormal fibrosis and slow conduction. However, only RV-PA conduit implantation or early PVR, and not late PVR, was associated with SCAI 3. This finding is in line with findings in the older rTOF population.[6]

After percutaneous pulmonary valve implantation in pediatric patients, an increase in premature ventricular contractions and nonsustained VTs have been reported, which resolved by 6 months.[26] These arrhythmias have been attributed to myocardial stretching and pinching of proximal stent struts into the RVOT, and its disappearance to formation of fibrosis.[26,27]

In a series of 32 patients with TOF morphological spectrum, primary RVOT stenting was performed as a palliative procedure before repair at a median age of 61 days.[28] In these patients, extensive fibrosis at the site of stent placement was reported, preventing complete removal of the stent in the majority. Likewise, in another series of 16 TOF patients (mean age: 28 ± 4 days) undergoing RVOT stenting as a palliative procedure, connective tissue surrounding the stent struts and focal inflammation was the common finding after removal of the stent.[29] Similarly, Happel et al[30] found marked fibrosis in all 4 specimens containing adjacent myocardial tissue after removal of an RVOT stent. These data may suggest that insertion of artificial material into the RVOT at a very young age may induce local fibrosis which may contribute to slow conduction within AI 3.

In longitudinal studies, complex TOF variants have been linked to all-cause mortality and VT/sudden cardiac death.[7,24] As shown in **Figure 2** and the **Central Illustration**, complex TOF variants more often required an RV-PA conduit/early PVR (77%) and were more often repaired via ventriculotomy (69%), making these determinants highly interrelated.

IMPLICATIONS FOR CLINICAL PRACTICE. The potential loss of accessibility to SCAI by catheter ablation after revalving is of concern. In the current series, all ablation failures were attributed to the overlying artificial material. Consequently, EPE before PVR has been implemented in our routine clinical protocol. The high prevalence of SCAI 3 in young patients with rTOF further supports this approach. Because the majority of induced and spontaneous VT in young patients with rTOF are related to SCAI 3, preventive ablation of SCAI 3 at the time of reoperation may be beneficial also in the young. Considering the lack of VT inducibility despite the presence of a substrate in very young patients, preventive ablation of a SCAI even without inducibility may be appropriate if the SCAI becomes inaccessible after surgery.

STUDY LIMITATIONS. The major limitation of our study is the small cohort of young patients with rTOF. Accordingly the observational analysis should be considered as hypothesis generating. Another limitation is the retrospective study design and conduction of the study in a single tertiary referral center. This factor could lead to bias in generalizability owing

to institution-specific protocols and patient selection. The majority of our patients were evaluated before reoperation and the findings may not be extrapolated to the general population with rTOF.

CONCLUSIONS

In young patients with rTOF, SCAI 3 was already present in almost one-third and the most prevalent substrate for spontaneous and inducible VT. Despite the presence of a SCAI 3, VT inducibility was low, compared with older patients with rTOF, which is important to consider if PES without mapping is used before revalving. Numbers are small, but complex TOF variants and inter-related type and timing of surgical interventions may contribute to SCAI 3 at young age. Inaccessibility of SCAI 3 after surgical PVR was the main reason for catheter ablation failure, supporting preventive ablation before or during re(re) valving of SCAI 3 also in the young.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors acknowledge the support from the Netherlands Cardiovascular Research initiative: An initiative with support of the Dutch Heart Foundation and Hartekind, CVON2019-002 OUTREACH. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The current study shows that a SCAI 3 is already present in approximately one-third of children and young adults with rTOF. Likely owing to the transpulmonary surgical approach used in most patients, no other SCAI location was found. In this young cohort, SCAI 3 was associated with complex TOF variants and potentially interrelated type and timing of surgical repair. Because SCAI 3 may become inaccessible for catheter ablation after PVR, the current study further supports the implementation of EPE and potentially preventive ablation in case of SCAI before PVR in young patients with rTOF.

TRANSLATIONAL OUTLOOK: Approximately one-half of children and young adults with rTOF and SCAI 3 were not inducible for VT at PES. Further studies are needed to investigate the cause of the lower VT inducibility despite the presence of SCAI, which may impact the value of PES without EAM for risk stratification before revalving at young age.

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KEY WORDS **ablation, congenital heart disease, pediatric cardiology, pulmonary valve replacement, tetralogy of Fallot, ventricular tachycardia**

APPENDIX **For a supplemental table, please see the online version of this paper.**