European Heart Journal (2017) **38**, 268–276
doi:10.1093/eurheartj/ehw202

Arrhythmogenic anatomical isthmuses identified by electroanatomical mapping are the substrate for ventricular tachycardia in repaired Tetralogy of Fallot

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Received 2 November 2015; revised 17 April 2016; accepted 27 April 2016; online publish-ahead-of-print 26 May 2016

See page 277 for the editorial comment on this article (doi:10.1093/eurheartj/ehw167)

Aims The majority of ventricular tachycardias (VTs) in repaired tetralogy of Fallot (rTOF) are related to anatomically defined isthmuses. We aimed to identify specific electroanatomical characteristics of anatomical isthmuses (AI) related to VT which may allow for individualized risk stratification and tailored ablation.

Methods and results Seventy-four consecutive rTOF patients (40 ± 16 years, 63% male) underwent VT induction and right ventricular electroanatomical voltage and activation mapping during sinus rhythm (SR) to identify the presence and characteristics of AI (isthmus width, length and conduction velocity index [CVi]). Twenty-eight patients were inducible for 41 VTs. All 74 patients had at least one AI. However, AI in patients with VT were longer (22 ± 7 vs. 16 ± 7 mm, $P = 0.001$), narrower (20 ± 8 vs. 28 ± 11 mm, $P < 0.001$) and had lower CVi (0.36 ± 0.34 vs. 0.78 ± 0.24 m/s, $P < 0.001$). Thirty-seven VTs in 24 patients were mapped (pace-, entrainment mapping, and/or VT termination by ablation) to 28 AI. All 28 AI related to VT had a CVi < 0.5 m/s (slow conducting AI (SCAI)). In contrast, 87 of 89 AI of the 46 patients without VT had CVi ≥ 0.5 m/s. Sixty-two patients were discharged without the presence of an SCAI (44 had no SCAI at baseline, 18 underwent ablation of the SCAI) and 10 still had an SCAI (no/failed ablation). During follow-up (50 ± 22 months), no patient without SCAI had any VT, which occurred in 5/10 patients with SCAI ($P < 0.001$).

Conclusion In rTOF, slow conducting anatomical isthmuses identified by electroanatomical mapping during SR are the dominant substrate for VT allowing individualized risk stratification and preventive ablation.

Keywords Congenital heart disease • Tetralogy of Fallot • Ventricular tachycardia • Electroanatomical mapping

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease across all age groups.[1] The prevalence among adults is increasing as a result of earlier and improved surgical interventions.[1,2] Despite early repair patients have a 29-fold higher risk for sudden death compared with the age-matched population.[3,4] Of concern, two-thirds of patients who die suddenly or experience life-threatening ventricular tachycardia (VT), typically early to middle-aged adults, have preserved cardiac function before the first event.[4–6]

Retrospective, observational studies have identified factors associated with VT; however, these have limited predictive value.[7] Earlier repair and progress in surgical techniques from a transventricular to a transatrial-transpulmonary approach may influence the VT substrate and its prediction. Large studies with long follow-up, required for validated risk stratification in patients repaired in the modern surgical era, will not be available in the near future.[8] Direct

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identification of the substrate for VT in an individual patient could overcome the problem of lacking clinical arrhythmia predictors and would allow personalized risk stratification.[9] Mapping studies performed in repaired TOF (rTOF) patients have identified re-entry as the dominant underlying VT mechanism.[10–12] Re-entry circuits are typically related to anatomically defined isthmuses bordered by unexcitable structures such as surgical scars, valve annuli, and patches.[10–12] Anatomical isthmuses are however present in almost all rTOF patients but not all are related to VT. We hypothesized that specific isthmus characteristics are required to constitute the substrate for re-entry VT. The overall aim for the study was to identify these arrhythmogenic isthmuses by electroanatomical mapping (EAM) allowing individualized risk stratification and tailored treatment.

Methods

Patient selection and study design

The study cohort consisted of consecutive rTOF patients, who were considered at risk for VT or had documented VT referred for electrophysiological evaluation and treatment between 2005 and 2013 (Leiden University Medical Center, Leiden, The Netherlands ($n = 52$); Bordeaux University Hospital, Bordeaux, France ($n = 22$)). Patients were considered at risk when at least one prior reported risk factor was present: syncope, QRS duration $\geq$180 ms, non-sustained VT on Holter, at least moderate dysfunction of the left ventricle (LV) or right ventricle (RV), late repair ($\geq$5years of age) and the presence of a transannular patch (TA-patch).[13–19] All patients were treated according to our standard clinical protocol (Supplementary material online, Supplemental A) and provided informed consent. Electrophysiological studies were only performed in rTOF patients considered at risk for VT, which is part of the clinical protocol; therefore, no ethical commission approval was required.

Medical records were reviewed for date and type of repair/re-operation and documented ventricular arrhythmias on 12-lead electrocardiograms (ECGs), Holter recordings or internal cardiac defibrillator (ICD) interrogation. Non-paced 12-lead ECGs were analysed for QRS duration. Transthoracic echocardiographic and cardiac magnetic resonance imaging studies were reviewed for assessment of biventricular function.

Electrophysiological evaluation consisted of programmed electrical stimulation (PES) to induce VT and detailed 3D-EAM during sinus rhythm (SR).

After venous puncture PES was performed using three drive CL (600, 500, and 400 ms) with up to three extrastimuli (down to 200 ms or refractory period) and rapid pacing from at least two consecutive RV sites, one close to the infundibular septum before and during isoproterenol infusion (2–10 μg/min). Electroanatomical mapping (Thermocool catheter; Biosense Webster, Inc., Diamond Bar, CA, USA) could be performed using the same venous access (using the QRS as reference for substrate mapping during SR and VT activation mapping). All contact points were saved together with local electrograms characteristics (peak-to-peak bipolar amplitude and local activation time, defined as sharp peak deflection of the local bipolar electrograms that coincides with the maximum down stroke of the local unipolar signal) and displayed color coded for local voltages or activation sequences on a shell of the RV. At low amplitude sites ($<$1.5 mV), pacing was performed with high output (10 mA/2 ms). Sites with pacing threshold $>$10 mA were considered unexcitable tissue due to surgical scars and patch material which together with valve annuli can form the boundaries of four potential anatomical isthmuses (AI) (*Figure 1A*).[10–12]

According to the clinical presentation and the results of PES patients were assigned to group 1 (no spontaneous VT, not inducible for VT), group 2 (no spontaneous VT, inducible for VT), and group 3 (spontaneous VT).

Characterization of anatomical isthmuses and its relation to ventricular tachycardia

Anatomical isthmuses were classified as 'electroanatomical normal' if normal bipolar electrograms ($\geq$1.5 mV) could be continuously recorded throughout the AI connecting to normal voltage areas. For each AI width (shortest distance between unexcitable boundaries) and length (distance between the first normal bipolar electrogram at each side of the AI, referred to as isthmus entrance and exit electrograms or length of the unexcitable boundaries) were measured using the software of the 3D-mapping system (CARTO XP^{TM}/CARTO 3^{TM}). The fill threshold for EAM of the AI was set at $\leq$10 mm and care was taken to delineate the length of the isthmus by recording the first normal voltage electrograms at isthmus entrance and exit. The conduction time through the isthmus during SR was defined as the difference between the local activation time at isthmus entrance and exit (*Figure 1B* and *C*). The conduction velocity index (CVi) was calculated (length/conduction time). Examples of electroanatomical-mapping data are provided in *Figure 2*.

Normal values for CVi were derived from 12 patients without structural heart disease referred for right ventricular mapping and ablation of idiopathic premature ventricular contraction (PVC).

For each induced VT, the critical part of the VT re-entry circuit and its spatial relationship to the identified AI was determined by either pace mapping (at 2 mA/2 ms up to 10 mA/2 ms until capture) within the isthmus ($\geq$11/12 ECG-lead match between VT-QRS and paced QRS) or by activation mapping and/or termination of VT by radiofrequency (RF) ablation, if VT ablation was indicated. Before ablation, a second venous access was obtained for a steerable quadripolar RV catheter. Ablation was considered successful if conduction through the corresponding AI was blocked after RF delivery and VT was no longer inducible.[10,11] In selected patients in whom pulmonary valve replacement (PVR) was recommended intraoperative cryoablation of the VT-related AI was performed. In patients without ICD at presentation, an ICD was implanted according to current guidelines.[20]

Isthmus characteristics were compared between groups to identify those isthmuses that constitute an arrhythmogenic substrate. In a second step, we compared the occurrence of spontaneous VT during follow-up between patients without an arrhythmogenic isthmus at baseline or after ablation (group A) and patients discharged with an arrhythmogenic isthmus (group B).

Follow-up

Patients were followed at the grown-up congenital heart disease outpatients' department and/or the arrhythmia service according to institutional protocols. Follow-up started at electrophysiological evaluation or (if performed) ablation. Mortality was assessed from hospital records.

Statistical analysis

Continuous data are reported as median with interquartile range or mean $\pm$ SD according to data distribution. Categorical data are presented as percentage or frequencies. Differences between the three groups were assessed by one-way ANOVA with *post hoc* testing, Kruskal–Wallis and χ^2 test where appropriate. The properties of VT-related

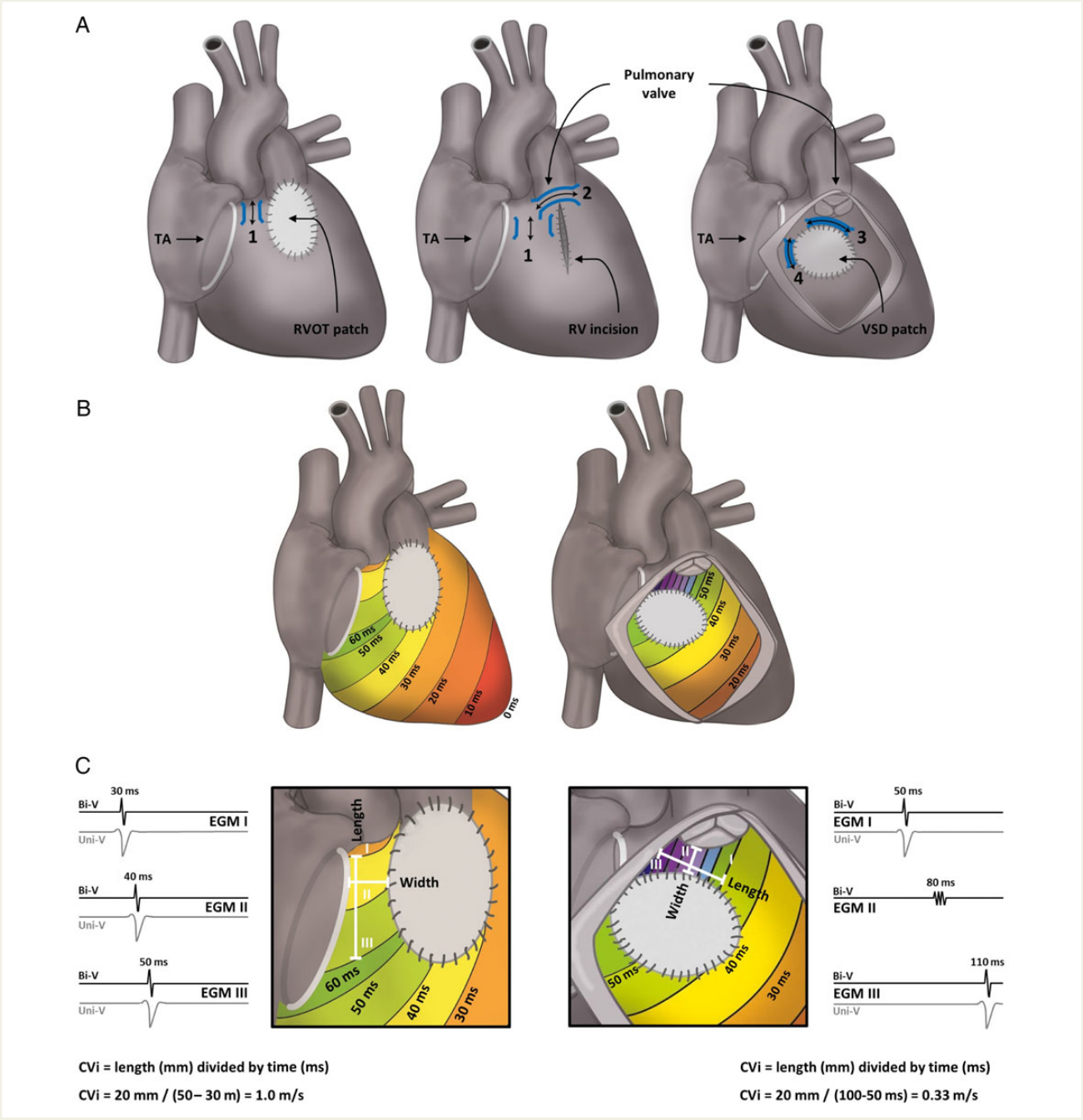

Figure 1 (*A*) Schematic overview of the four potential anatomical isthmuses (blue brackets), isthmus 1 bordered by tricuspid annulus and right ventricular outflow tract patch/right ventricular incision, isthmus 2 by right ventricular incision and pulmonary valve, isthmus 3 by pulmonary valve and ventricular septal defect patch, isthmus 4 by ventricular septal defect patch and tricuspid annulus. (*B*) Schematic activation of the right ventricle during SR displayed as colour-coded isochronal (10 ms) map from red (early activation) to purple (latest activation). (*C*) Enlarged views of anatomical isthmus 1 (left) and 3 (right) with corresponding electrograms recorded from sites I–II–III, as indicated. Isthmus width, distance between unexcitable anatomical boundaries; isthmus length, distance between normal electrograms (I and III) recorded at entrance and exit site of the anatomical isthmus. Conduction time through the anatomical isthmus, difference in local activation time between the entrance and exit of the anatomical isthmus. Conduction velocity index calculated as indicated. EGM, electrogram; RVOT, right ventricular outflow tract; RV, right ventricular; VSD, ventricular septal defect.

AI and anatomical isthmuses of patients without VT were compared using a χ^2 or Mann–Whitney *U* test where appropriate and were illustrated with a dot plot. To determine the association between the presence of an arrhythmogenic isthmus and clinical variables (age of repair, time after repair, gender, transannular patch, syncope, QRS duration, nsVT on Holter, and RV/LV function), odds ratios including

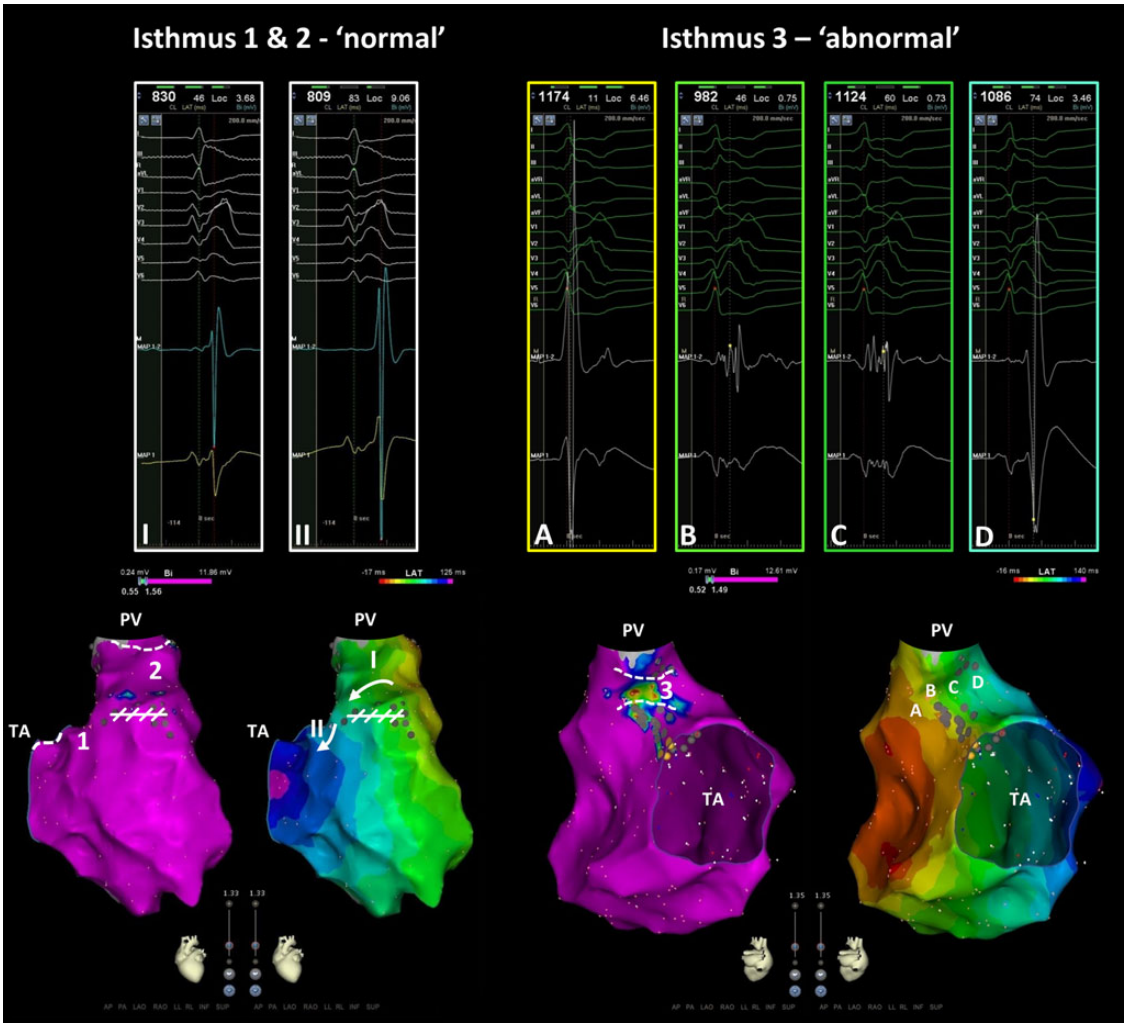

Figure 2 Electroanatomical assessment of anatomical isthmus 1 (between tricuspid annulus and right ventricular incision), isthmus 2 (between right ventricular incision and pulmonary valve), and isthmus 3 (between pulmonary valve and ventricular septal defect patch). On the left, an example of electroanatomical normal isthmuses 1 and 2 in a patient without inducible ventricular tachycardia. Upper panel: Normal bipolar electrograms with a peak-to-peak amplitude of ≥1.5 mV recorded from isthmus 1 (site II) and isthmus 2 (site I). Lower panel: 3D electroanatomical reconstruction of the right ventricle (anterior view) displayed as colour-coded voltage map (left, purple indicates normal voltages) and activation map (right, red indicates early activation, purple late activation). The grey tags (electrically unexcitable scar) correspond to a previous right ventricular incision (marked with the white line). Isthmus 1 had a width of 46 mm (tricuspid annulus to right ventricular incision) and a length of 10 mm, isthmus 2 a width of 37 mm (right ventricular incision to pulmonary valve) and length of 27 mm. On the right, isthmus 3 of a patient with inducible ventricular tachycardia (cycle length 250 ms) is shown. Upper panel: electrograms recorded through isthmus 3 (sites A–B–C–D) are shown as indicated. The first and last electrogram (A&D) are 'normal', the second and third electrogram (B&C) are 'abnormal' (<1.5 mV). Lower panel: 3D electroanatomical reconstruction of the right ventricle (posterior view) displayed as voltage map and activation map. The grey tags correspond with the ventricular septal defect patch. Isthmus 3 (delineated by the white dashed line) had a width of 12 mm and length of 27 mm. The time interval between A and D was 62 ms resulting in a conduction velocity index of 0.44 m/s. Isthmus 3 was related to the induced ventricular tachycardia based on pace-mapping. EGM, electrogram; PV, pulmonary valve; RV, right ventricle; TA, tricuspid annulus; VSD, ventricular septal defect; VT, ventricular tachycardia.

95% confidence intervals were estimated using uni and multivariable logistic regression. The occurrence of VT during follow-up was compared for group A (patients without an arrhythmogenic isthmus at baseline or after ablation) and group B (patients discharged with an arrhythmogenic isthmus) using a log-rank test. SPSS 20.0 for Windows was used. *P*-values were two sided and considered statistically significant if <0.05.

Results

Patients

Seventy-four patients (age 40 ± 16 years, 64% male) repaired at a median age of 5.9 years (2.3–11.8) were included; in 44 (59%), biventricular function was preserved. Twenty-eight (38%) patients

Table 1 Baseline characteristics

Characteristics	No VT ($n = 46$)	VT inducible ($n = 15$)	VT spontaneous and inducible ($n = 13$)	Overall P
Age (year)	35.1 ± 14.7	42.8 ± 12.4	52.3 ± 14.8*	0.001
Male, *n* (%)	28 (61%)	10 (67%)	9 (69%)	0.824
Age at repair (year)	5.3 (2.0–6.9)	5.5 (1.7–16.3)	13.4 (5.8–19.8)*	0.005
Age at repair ≥5 year	25 (54%)	9 (60%)	11 (85%)	0.142
TA-patch	19/39 (49%)	7 (47%)	5/11 (46%)	0.978
Time after repair (year)	29.5 ± 11.1	33.5 ± 8.7	36.9 ± 9.4	0.062
PVR	8 (17%)	6 (40%)	4 (31%)	0.174
Age at PVR age (year)	30.6 ± 10.4	40.9 ± 15.9	26.1 ± 11.0	0.181
Syncope	3 (7%)	1 (7%)	1 (8%)	0.989
QRSd non-paced (ms)	155 ± 25	161 ± 25	149 ± 32	0.510
QRSd ≥180 ms	6/44 (14%)	3/13 (23%)	2/11 (18%)	0.705
Non-sustained VT	12/41 (29%)	3/11 (27%)	3/7 (43%)	0.745
ICD carrier	1 (2%)	1 (7%)	4 (31%)*	0.004
LV function				
Good/mildly depressed	46 (100%)	14 (93%)	11 (85%)*	0.039
Moderately/severely depressed	0 (0%)	1 (7%)	2 (15%)	
RV function				
Good/mildly depressed	28 (61%)	9 (60%)	7 (54%)	0.900
Moderately/severely depressed	18 (39%)	6 (40%)	6 (46%)	
Preserved cardiac function, *n* (%)	28 (61%)	9 (60%)	7 (54%)	0.900
Risk factor, *n*	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–3.0)	0.085

LV, left ventricle; PVR, pulmonary valve replacement; QRSd; QRS duration; RV, right ventricle; TA, transannular; VT, ventricular tachycardia.
*$P < 0.01$ vs. controls.

Table 2 Presence and characteristics of anatomical isthmuses according to ventricular tachycardia profile

Characteristics	No VT ($n = 46$)	VT inducible ($n = 15$)	VT spontaneous and inducible ($n = 13$)	Overall P
Isthmus, *n*	2.0 (1.0–2.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.111
Minimal width (mm)	28 ± 11	22 ± 10	18 ± 5*	0.005
Maximal length (mm)	16 ± 7	20 ± 7	25 ± 7*	0.001
EA abnormal isthmus, *n* pts	5	13*	13*	<0.001
Lowest CVi (m/s)	0.78 ± 0.24	0.44 ± 0.44*	0.27 ± 0.09*	<0.001

CVi, conduction velocity index; EA, electroanatomical; VT, ventricular tachycardia.
*$P < 0.01$ vs. no. of VT.

had one, 29 (39%) had two, and 17 (23%) had ≥3 risk factors for VT; 13 patients had a documented VT. During PES, 28 patients, including all 13 with prior VT, were inducible for 41 VTs [median of 1 (1–2), VTCL 252 ms (231–312)]. Patient characteristics according to clinical presentation and the results of PES are summarized in *Table 1*.

Presence and characteristics of anatomical isthmuses according to groups

In all patients at least one AI could be identified during sinus rhythm (69 ± 14 bpm) in 70 patients or RV pacing in four patients (*Table 2*). An electroanatomical abnormal isthmus (bipolar voltages <1.5 mV) was found in 26 of 28 patients with inducible VT, but in only 5/46 patients without VT. Anatomical isthmuses of patients with clinical and/or induced VT were on average 8 mm (95% CI 3–13, $P = 0.002$) narrower and 6 mm (95% CI 2–9, $P = 0.001$) longer compared with AI of patients without VT. The most prominent difference in isthmus characteristics was the conduction velocity index, which was significantly lower in patients with clinical and/or induced VT (0.36 ± 0.34 vs. 0.78 ± 0.24, $P < 0.001$). Notably, there was no significant difference in isthmus length, width, and conduction

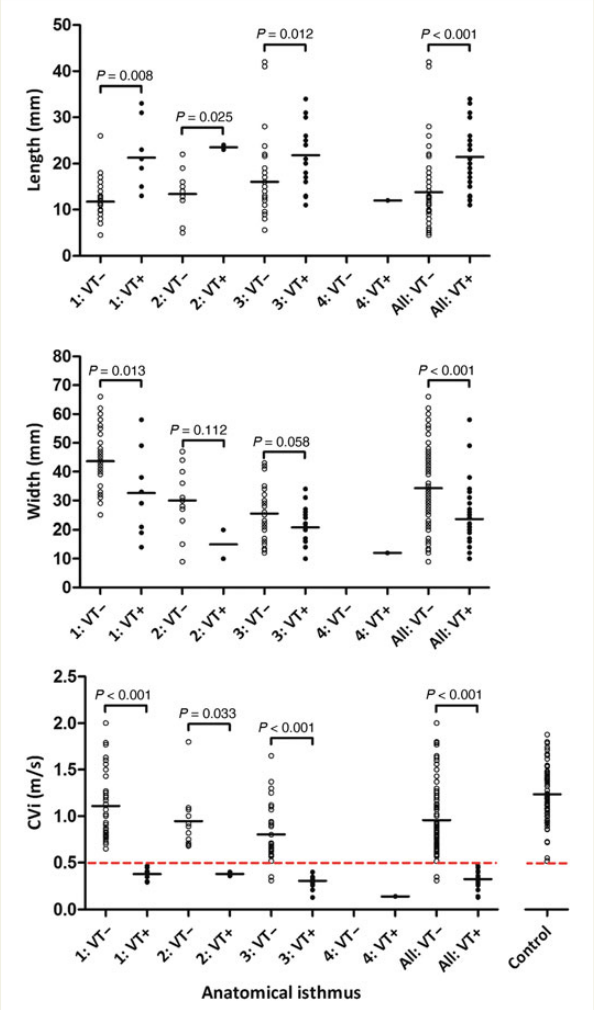

Figure 3 Aligned dot plot. CVi, conduction velocity index; numbers 1–4 indicate anatomical isthmus 1–4; VT, ventricular tachycardia; VT−, isthmus not critical for VT; VT+, isthmus critical for ventricular tachycardia.

velocity index between patients with only inducible VT (group 2) and patients with spontaneous VT (group 3). Conduction velocity index was not related to age (additional data are provided in Supplementary material online, Supplemental B1). Detailed data for each AI is provided in Supplementary material online, Supplemental B2. No mapping related complications occurred.

Conduction velocity index in controls

Conduction velocity index were calculated from 142 adjacent RV outflow tract sites (distance between sites 22 ± 9 mm) in 12 patients (age 41 ± 13 years, 33% male) without structural heart disease. The average CVi during SR (67 ± 10 bpm) was 1.24 ± 0.32 m/s (range 0.52–1.89 m/sec) with 95% of all CVi >0.56 m/s. The slowest CVi in controls were measured in a control with right bundle branch block (0.92 ± 0.43 m/s, range 0.52–1.68 m/s). Based on these findings a CVi <0.5 m/s was considered abnormal.

Table 3 Association between risk factors and presence of arrhythmogenic isthmuses

	Arrhythmogenic isthmus univariate odds ratio (95% CI)	P
Gender (male)	1.06 (0.40–2.81)	0.914
Age at repair, per year↑	1.07 (1.00–1.15)	0.037
Time after repair, per year↑	1.06 (1.01–1.11)	0.029
TA-patch	0.79 (0.29–2.14)	0.638
Syncope	1.10 (0.17–7.04)	0.918
QRS duration (ms)	1.00 (0.98–1.02)	0.858
nsVT on Holter	1.74 (0.54–5.61)	0.357
RV function depressed	0.92 (0.35–2.40)	0.864
LV function depressed	Indefinite	
Risk factor	1.21 (0.73–1.99)	0.460

LV, left ventricular; ms, milliseconds; nsVT, non-sustained VT; TA-patch, transannular patch; VT, ventricular tachycardia; RV, right ventricular.

Characteristics of VT-related anatomical isthmuses

Thirty-seven of 41 induced VTs were related to an AI; 24 VTs in 17 patients were mapped to isthmus 3, 10 VTs in 8 patients to isthmus 1, 2 VTs in 2 patients to isthmus 2, and 1 VT to isthmus 4. Twenty patients had only one VT-related AI and four patients had two VT-related AI each supporting different VT re-entry circuits. Ventricular tachycardia-related AI were significantly longer and tended to be narrower than isthmuses in patients without VT (*Figure 3*). All VT-related AI were electroanatomical abnormal and slow conducting with a CVi of <0.5 m/s (slow conducting or arrhythmogenic AI). Such a slow conducting anatomical isthmus (SCAI) was only found in two patients of group 1.

Four VTs in four patients could not be related to an AI. In two patients, both with advanced heart failure and poor RV function and no SCAI, the VT substrate was related to a large free wall scar ($n = 1$) and likely due to a focal VT mechanism ($n = 1$). In two patients with an arrhythmogenic isthmus sufficient mapping could not be performed to prove the relation of the induced VT to an identified slow conducting isthmus due to procedural reasons. The sensitivity and specificity of an SCAI with CVi < 0.5 m/s to predict AI-related VT was 93 and 100%, respectively.

Association between risk factors and arrhythmogenic isthmuses

On univariable analysis, age at repair (OR 1.07 (1.00–1.15)/year, $P = 0.037$) and time after repair (OR 1.06 (1.01–1.11)/year, $P = 0.029$) were associated with the presence of a slow conducting AI. In multivariable analyses, none of the variables remained associated with an SCAI. Additional information is provided in *Table 3*.

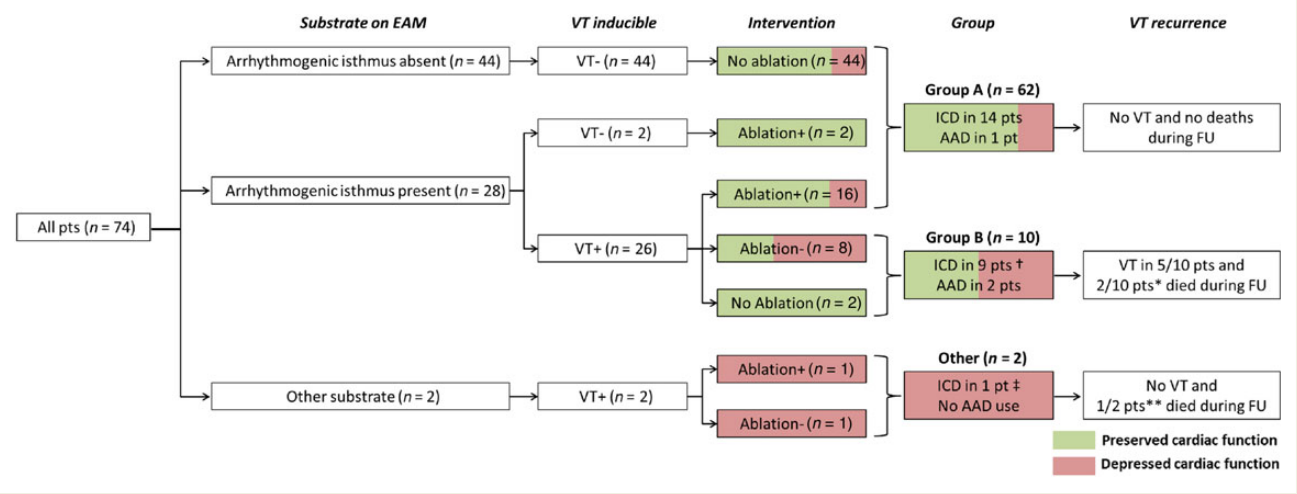

Figure 4 AAD, antiarrhythmic drugs; Ablation+, complete successful ablation; Ablation-, no complete successful ablation; FU, follow-up; ICD, internal cardiac defibrillator; Pt (s), patient (s); VT, ventricular tachycardia; †, no ICD because of physician preference; ‡, no ICD because of mental disability; *, heart failure; **, cancer.

Ablation targeting arrhythmogenic anatomical isthmuses

Sixteen of 26 patients with an arrhythmogenic isthmus-related VT and the two patients with a slow conducting isthmus but without induced VT underwent successful isthmus ablation. A total of 62 patients (44 without arrhythmogenic AI at baseline, 18 after successful isthmus ablation) were discharged without slow conducting isthmus (group A). In the remaining 10/26 patients (group B) with an arrhythmogenic isthmus and VT, VT-ablation was not successful ($n = 8$) or not performed ($n = 2$). The two patients with heart failure and inducible VT that were not related to an AI (group C) underwent ablation, which was successful in one. Eighteen patients (49 ± 14 years, 72% male) received an ICD before discharge; in six patients VT-ablation has failed and was not performed in two. In additional six patients, an ICD was implanted despite procedural success because of a depressed cardiac function ($n = 2$) or patients preference. The remaining four patients received an ICD because of a depressed cardiac function ($n = 3$) and a prior out-of-hospital cardiac arrest ($n = 1$).

Follow-up

Patients were followed for a mean of 50 ± 22 months. All 63 patients without a slow conducting isthmus at discharge remained free from VT (group A). Five of 10 patients with a failed ablation of an arrhythmogenic, slow conducting isthmus (group B) experienced $1 \geq$ episodes of VT (all terminated with ICD therapy), *Figure 4*. The difference between groups A and B was significant ($P < 0.001$). Three patients died during follow-up, two due to terminal heart failure one due to cancer. No sudden cardiac death occurred.

Discussion

To the best of our knowledge, this is the first study to present substrate identification for VT in patients with rTOF with the potential for individualized risk stratification and immediate tailored treatment. We found that slow conducting AI (<0.5 m/s) were the substrate for all documented and induced VT in rTOF with *preserved* cardiac function. This substrate could not be predicted by previously suggested clinical risk factors. Repaired TOF patients without an arrhythmogenic, slow conducting AI at baseline or after successful isthmus ablation were free of VT during a mean follow-up of 50 ± 22 months.

Ventricular arrhythmias in repaired tetralogy of Fallot

The majority of arrhythmias documented in young to middle-aged patients with rTOF are fast but monomorphic VTs, which is in line with the short median VTCL of 252 ms (231–312) observed in our cohort.[9] These arrhythmias are likely to be fatal if untreated, even in patients with good biventricular function. Of concern and importance, two-thirds of rTOF patients that die suddenly, typically also early to middle-aged adults, have preserved cardiac function and good functional status prior to the event, comparable with our study population, supporting non-heart failure related arrhythmia mechanisms.[4,5] Clinical parameters have been associated with VT and sudden cardiac death but the predictive value is limited and may not apply to the current rTOF population with earlier and improved surgical interventions.[7] Identification of the VT substrate in an individual patient may allow individualized risk stratification and substrate-based treatment.

Substrate for ventricular tachycardia

Mapping studies in patients with rTOF and spontaneous VT have demonstrated that the substrate is typically located in anatomically defined isthmuses.[10–12] Anatomical isthmuses are the result of the malformation and the type of repair and were present in all rTOF patients in our cohort. In our study, AI 1 and 3 were the most prevalent AI. Isthmus 3 was the narrowest isthmus, which is in line with the observation in postmortem specimen of rTOF.[21] Of interest,

AI 3 when compared with the other isthmuses was more often electroanatomical abnormal and more often related to VT. In the postmortem histological analysis, isthmus 3 had the highest degree of fibrosis thereby providing the potential histological substrate for slow conduction. We could demonstrate that specific electroanatomical isthmus characteristics, in particular the conduction velocity index through an AI are the key determinants for VT. All VT-related AI had an abnormal, low conduction velocity index of <0.5 m/s.

Patients without a slow conducting isthmus at baseline or after ablation remained VT free during a follow-up of 262 patient years. Reported arrhythmia event rates in patients with similar clinical risk factors who have received ICDs for primary or secondary prevention ranged between 8% and 10% per year, which is comparable with the event rate in patients discharged with an arrhythmogenic isthmus.[9] These findings further support the strong link between slow conducting isthmuses and arrhythmia events.

Risk stratification in the modern era

The progress in surgical techniques from a classical transventricular to a transatrial-transpulmonary approach affects presence and geometry of the AI 1 and 2. However, isthmus 3 between the ventricular septal defect patch and the pulmonary valve is not prevented by current surgical techniques. This isthmus was present in 14 of the 15 patients in our cohort corrected within the first 2 years of life. Of importance, despite early repair, isthmus 3 was slow conducting in five (33%) and related to VT in four (27%) of these patients.

The proposed method of substrate identification using a non-fluoroscopic mapping system requires a single venous access and can be applied for individualized VT risk stratification with minimal radiation exposure. This is especially valuable for patients with preserved cardiac function and no competing arrhythmia mechanism, who, importantly constitute the majority of the rTOF population. In patients with an arrhythmogenic isthmus preventive ablation may be considered, which can be performed during the same procedure or intra-operatively for those who require a second surgical interventions for PVR. The main reasons for ablation failure in our study were hypertrophy of isthmus 3 ($n = 3$) and the presence of a pulmonary homograft covering isthmus 3 ($n = 2$). Repaired TOF patients without an arrhythmogenic isthmus at baseline or after successful isthmus ablation, in the presence of a preserved biventricular function, may not require ICD implantation.

Limitations

The current study is limited by sample size, although, to our knowledge, this is the largest cohort of rTOF patients that underwent VT induction and EAM to date. Our study is also limited by a mean follow-up of 50 ± 22 months, although supporting evidence is provided that conduction velocity of the majority of AI may not change during follow-up. Wider AI with preserved myocardium and normal voltages are unlikely to change conduction properties, which were not age dependent in our cohort, provided that cardiac and valvular functions remain stable. In contrast, narrower isthmuses with abnormal voltages may need re-mapping or may even justify preventive isthmus ablation in particular if CVi are low. However, sequential mapping was not performed to evaluate isthmus characteristics over time.

Studies with longer follow-up to further validate the concept are desirable. This study has been performed in high-volume tertiary referral centres with expertise in electrophysiological evaluation of patients with congenital heart disease, which likely influences the characteristics of the patient population. Furthermore, contact force catheters became available only during the course of the study and were therefore used in the minority of patients. Without contact force measurement some sites with low voltage and no-capture due to poor contact may have been tagged as unexcitable tissue thereby underestimating isthmus widths.

Conclusion

In rTOF, slow conducting AI are the dominant substrate for VT and can be identified by EAM via a single venous access allowing individualized risk stratification and tailored treatment.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

G.F.L.K., O.M.D., A.P.W., K.Z. performed statistical analysis. K.Z. handled funding and supervision. G.F.L.K., F.S., M.W., Z.J., A.P.W., K.Z. acquired the data. G.F.L.K., F.S., O.M.D., Z.J., A.P.W., K.Z. conceived and designed the research. G.F.L.K., K.Z. drafted the manuscript. G.F.L.K., F.S., O.M.D., M.W., N.A.B., J.-B.T., N.D., M.J.S., Z.J., A.P.W., K.Z. made critical revision of the manuscript for key intellectual content.

Acknowledgements

We thank W.G. Stevenson, MD for his insightful comments throughout the study and Ron Slagter for the design of *Figure 1*.

Conflict of interest: The department of cardiology (LUMC) receives unrestricted research grants from Boston Scientific, Medtronic, and Biotronik. F.S. receives speaking honorarium from St Jude Medical, Biosense Webster, Medtronic, Sorin group, Bayer Healthcare, Boehringer Ingelheim, and consulting fees from St Jude Medical, Bayer Healthcare.

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