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Ventricular Tachycardia in Repaired Tetralogy of Fallot

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Citation

Kapel, G. F. L. (2018, June 6). *Ventricular Tachycardia in Repaired Tetralogy of Fallot*. Retrieved from <https://hdl.handle.net/1887/64018>

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Cover Page



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Author: Kapel, G.F.L.

Title: Ventricular Tachycardia in Repaired Tetralogy of Fallot

Issue Date: 2018-06-06

VENTRICULAR TACHYCARDIA IN REPAIRED TETRALOGY OF FALLOT

Risk Stratification and Invasive Treatment

Gijsbert Floris Lodewijk Kapel

The research described in this thesis was performed at the department of Cardiology of the Leiden University Medical Center, Leiden, the Netherlands.

Cover design: Off Page Amsterdam

Layout and print production: Off Page Amsterdam

ISBN: 978-94-6182-878-1

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Financial support to the costs associated with the publication of this thesis from Abbott Medical Nederland B.V., BIOTRONIK Nederland B.V., Canon Medical Systems Nederland, ChipSoft, Pfizer B.V. and Servier Nederland Farma B.V. is gratefully acknowledged.

VENTRICULAR TACHYCARDIA IN REPAIRED TETRALOGY OF FALLOT

Risk Stratification and Invasive Treatment

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdediging op woensdag 6 juni 2018
klokke 15:00 uur

door

Gijsbert Floris Lodewijk Kapel
geboren te Leiderdorp in 1986

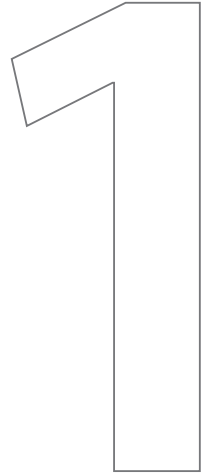
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Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Aan mijn ouders en Maaïke

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General Introduction, Aim and Outline of the Thesis

ANATOMY OF TETRALOGY OF FALLOT

Tetralogy of Fallot (TOF) is characterized by four anatomical lesions: pulmonary and/or sub-pulmonary stenosis, ventricular septal defect (VSD), overriding of the aortic orifice and concentric right ventricular (RV) hypertrophy as a secondary feature.^{1, 2} In 1888 Arthur Fallot published his well-known paper describing the combination of these four anatomical features in “la maladie bleue”.³ From a pathophysiological point of view, the dominant feature of TOF is the anterior deviation of the outlet septum.^{1, 2, 4} This deviation results in a sub-pulmonary stenosis, sub-aortic VSD and dextraposition of the aorta overriding the ventricular septum.^{1, 2} These features cause RV pressure and volume overload resulting in concentric RV hypertrophy. The outlet septum is part of the supraventricular crest, and in normal hearts forms a continuum with the ventriculo-infundibular fold and the trabeculo septomarginalis (Figure 1a, normal RV). In TOF as compared to the normal heart, the outlet septum is recognizable as a separate structure, due to the above mentioned anterior deviation (Figure 1b, tetralogy of Fallot). The morphology of the outlet septum in TOF varies considerably. The thickness of the outlet septum varies from severe hypertrophied myocardium to fibrous tissue.^{1, 2} TOF is also associated with other lesions, for example atrial septal defect (also known as Pentalogy of Fallot), atrioventricular septal defect (associated with Down syndrome), anomalies of coronary arteries (especially a so-called conal branch crossing over the right ventricular outflow tract (RVOT)), and stenosis of the pulmonary trunk and pulmonary arteries, possibly related to lack of flow through the narrowed outflow tract during development.¹

REPAIR OF TETRALOGY OF FALLOT

After introduction of the cardiopulmonary bypass by Gibbon in 1953, Lillehei was in 1954 the first to perform intracardiac repair of TOF at the University of Minnesota.⁵⁻⁷ During TOF

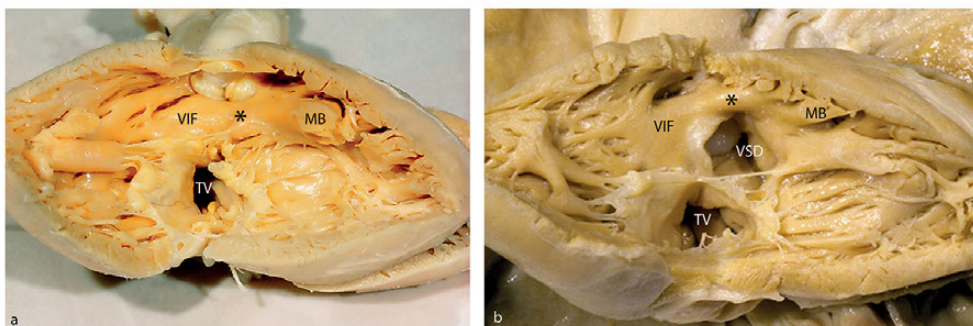


Figure 1. Overview of the right ventricle of a normal hart (panel A) and a tetralogy of Fallot heart (panel B), please note that the outlet septum (*) is recognizable as a separate structure in tetralogy of Fallot. *, outlet septum; MB, moderator band (i.e. trabeculo septomarginalis); TV, tricuspid valve; VIF, ventriculo-infundibular fold, VSD, ventricular septal defect. Figure 1 by courtesy of Department of Anatomy & Embryology, LUMC.

repair, the sub-aortic VSD is closed with a patch. To prevent damage to the His-bundle, care is taken to stitch some millimetres away from the edge of the post-inferior rim of the VSD, which is most often perimembranous, but can also be muscular.^{8, 9} The infundibular right ventricular outflow tract obstruction is relieved by resection of infundibular muscle, valvular RVOT obstruction is relieved by commissurotomy of the pulmonary valve and/or incision of the pulmonary annulus with augmentation by using a transannular patch.⁸ Initially, repair of TOF was performed via a large RV incision and frequently with the use of a large transannular patch. The RV incision and transannular patch, which may result in significant pulmonary insufficiency, are associated with chronic RV volume overload, RV dilation, RV dysfunction and arrhythmias.^{8, 10} Therefore, a transatrial-transpulmonary approach has been introduced and RV incision is largely omitted. In case of a narrow pulmonary annulus, a small transannular RVOT patch is still required during transatrial-transpulmonary repair. Presently, most TOF patients undergo transatrial-transpulmonary repair in the first year of life.^{8, 11}

EPIDEMIOLOGY OF TETRALOGY OF FALLOT

TOF is the most common cyanotic congenital heart disease, both the incidence and prevalence in children is currently 0.4 per 1000 live-births/children. The prevalence of adults with TOF has doubled from 0.1 to 0.2 per 1000 adults between 1980 and 2010 and is expected to increase further.¹²⁻¹⁴ This increased prevalence in adults is due to the favourable surgical outcome. Nevertheless, the risk for sudden death in TOF patients (5 per 1000 patient years) is still 29-fold higher compared with an age-matched population.^{15, 16} Of importance, two-thirds of TOF patients who die suddenly or experience ventricular tachycardia (VT) are young to middle-aged adults with a preserved cardiac function.¹⁶⁻¹⁸

VENTRICULAR ARRHYTHMIAS IN TETRALOGY OF FALLOT

The burden of ventricular arrhythmias in adults with TOF is considerable with a prevalence of 14.6% (14.2% VT and 0.5% ventricular fibrillation(VF)), observed in cohort of 556 adult TOF patients with mean age of 37±12 years.¹⁹ Ventricular arrhythmias encompass monomorphic VT, polymorphic VT and VF. ICD interrogation in TOF patients who have received an ICD for either primary or secondary prevention demonstrated that 82% of the ventricular arrhythmias that required ICD therapy were monomorphic, fast VT with an average of 213 beats per minute (bpm).²⁰ These fast monomorphic VT can even be fatal in TOF patients with a preserved cardiac function. Two previous studies in TOF patients who were referred for radiofrequency catheter ablation (RFCA) of symptomatic spontaneous VT demonstrated that 24 of 26 (92%) spontaneous and induced VT were macro-re-entrant VT. The critical re-entry sites of these macro-re-entrant VTs were located within anatomical isthmuses.^{21, 22} The anatomical isthmuses in TOF are the result of the malformation itself or of the surgical repair and are bordered by valve annuli, RV-incision scar and/or patch material. Four potential anatomical isthmuses have been described, see Figure 2.²² A post-mortem morphological study about isthmus presence and dimensions in repaired TOF demonstrated

that all 27 TOF patients had at least one anatomical isthmus.²³ This post-mortem study did not relate anatomical isthmus presence and dimensions to the timing and mode of repair which is relevant for present and future repaired TOF patients and therefore needs further study. It has been demonstrated that in TOF, the infundibular myocardium showed cellular hypertrophy, endocardial thickening and interstitial fibrosis at the time of repair, which extent was positively associated with the time of repair.²⁴ The pre-existing degenerative changes of the infundibular myocardium, cyanosis and pressure overload before repair and volume overload after repair might result in slow conduction which is critical for re-entry VT. The combination of anatomical isthmuses and histopathological changes may explain that anatomical isthmus related VT is the dominant mechanism for ventricular arrhythmias in TOF.

RISK STRATIFICATION FOR VT IN TETRALOGY OF FALLOT

Many retrospective observational studies have reported risk factors for VT in TOF. These risk factors include: the presence of a transannular patch, late repair (≥ 5 years of age), syncope, increase in QRS duration especially ≥ 180 ms, non-sustained VT on Holter, moderate to severe pulmonary regurgitation, at least moderate dysfunction of the left ventricle or right ventricle, left ventricular longitudinal dysfunction and extensive ventricular fibrosis on cardiac MRI.^{10, 16, 26-32} One of the first, most well-known and frequently used non-invasive risk factor in TOF is QRS duration. QRS duration is positively associated with ventricular arrhythmias and sudden death.^{28, 29} QRS duration prolongation in TOF can for example be due to right bundle branch block (RBBB) as result of the surgical repair or be due to increase

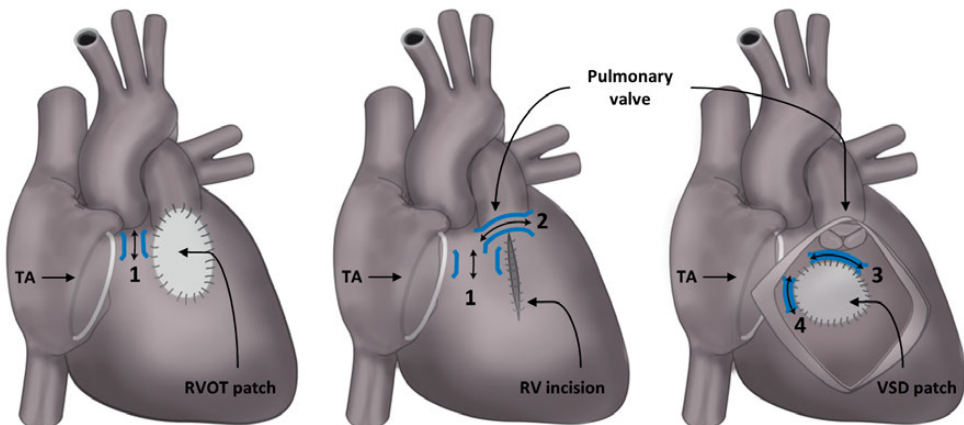


Figure 2. Overview of the four potential anatomical isthmuses in Tetralogy of Fallot. The 1st anatomical isthmus is located between the tricuspid annulus (TA) and RV-incision/RVOT-patch, the 2nd anatomical isthmus between the RV-incision (or patch) and pulmonary valve (PV), the 3th anatomical isthmus between the PV and VSD-patch and the 4th anatomical isthmus between the VSD-patch and tricuspid annulus. Reprinted from Kapel et. al.²⁵

in RV size/dilation.^{28, 33} However, the exact contribution of the VT substrate to QRS duration is yet unclear. The reported risk factors are used to select TOF patients to receive an ICD for primary prevention. However, in TOF patients who received an ICD for primary prevention, the percentages of appropriate therapy (8% per year) and disabling inappropriate ICD shocks (6% per year) demonstrate that risk stratification for the individual TOF patient is far from perfect and needs to be improved.^{20, 34} Larger studies with sufficient follow-up and validated risk stratification are unlikely to become available in the near future.³⁵ Therefore, further study of the VT substrate as related to outcome in TOF is desirable.

INVASIVE TREATMENT OF VT IN TETRALOGY OF FALLOT

The data available on RFCA of VT in TOF is limited, an overview of case series and cohort studies is provided in table 1.^{21, 22, 36-40} In TOF, VTs are fast (mean of 213 bpm) and subsequently often hemodynamically poorly tolerated limiting the time available for activation mapping during VT.²⁰ To avoid this problem, most of the earlier studies included only TOF patients with relatively slow VTs (mean of 172 bpm).³⁷⁻³⁹ To overcome the limited time available for activation mapping of fast VT in TOF, the two most recent cohort studies used substrate mapping to target fast VT (mean of 222 bpm) requiring very little time of activation mapping or even rendering activation mapping unnecessary.^{21, 22}

Substrate based ablation can be performed with contact mapping as demonstrated by Zeppenfeld et al.²² First VT is induced (three basis cycle length with up to three extra stimuli from at least two sites; RV apex and RVOT) to obtain QRS morphology. Second, during sinus rhythm, a 3D electroanatomical bipolar voltage map of the RV is constructed to identify the boundaries of the anatomical isthmuses (i.e. surgical scars, patch material and valve annuli; figure 2). Bipolar voltages of >1.5mV are considered normal. In areas with bipolar voltage <1.5mV, high output pacing (up to 10mA, 2 ms) is performed. If high outpacing does not capture, these areas are tagged as electrically unexcitable scar (EUS) consistent with surgical scars and patch material. After identification of the anatomical isthmuses, the critical re-entry circuit isthmus of the induced VT can be identified by activation mapping (diastolic activity during VT and slowing or termination during radiofrequency (RF) ablation), by entrainment during VT or by pace-mapping (pace-match, $\geq 10/12$ leads) if VT cannot be hemodynamically tolerated. If the critical re-entry circuit isthmus site is located within an anatomically defined isthmus, the anatomical isthmus is transected with a linear radiofrequency lesion until bidirectional block can be demonstrated.

Substrate based ablation can also be performed via non-contact mapping as demonstrated by Kriebel et al.²¹ First, a catheter is used to construct a RV map. Thereafter, a multi-electrode balloon that simultaneously records virtual unipolar electrograms is used. On the RV map, low voltage areas are identified that can serve as areas of conduction block during macro re-entrant VT (i.e. boundaries of the anatomical isthmuses). Thereafter, VT is induced and VT propagation is traced throughout the whole RV theoretically during one heart beat permitting fast mapping of hemodynamically unstable VTs. In the majority

Table 1. Overview of currently available case series and cohort studies of radiofrequency catheter ablation of VT in Tetralogy of Fallot.

Author, year	CHD type (n)	Pts (n)	Method	VTCL (ms)	Acute success	Recurrence	Follow-up (months)
Case series							
Burton ³⁶ , '93	TOF (2)	2	PM	270±28	2/2	0/2	4±3
Horton ³⁹ , '97	TOF (2)	2	AM + LL	430±71	2/2	0/2	11±0
Cohort							
Gonska ³⁸ , '96	TOF (7), PS (2), VSD (1), VSD+TGA (1)	11	AM	377±74	9/11	2/11	20±9
Morwood ⁴⁰ , '04	TOF (8), VSD (3), other (3)	14*	x	x	10/20	4/10‡	x
Furushima ³⁷ , '05	TOF (4), DORV (3)	7	AM + LL	346±77	4/7	6/7	61±29
Kriebel ²¹ , '07	TOF (10)	10	SM + LL	270±40	8/10	2/8‡	35
Zeppenfeld ²² , '07	TOF (9), AVSD (1), VSD+TGA (1)	11	SM + LL + IMG	276±78	11/11	1/11	30±29

*, 14 patients with 20 procedures; ‡, patients with acute success; AM, activation mapping; AVSD, atrioventricular septal defect; CHD, congenital heart disease; DORV, double outlet right ventricle; IMG, image integration using CT; LL, linear lesion; PM, pace-mapping; PS, pulmonary stenosis; Pts, patients; SM, substrate mapping; TGA, transposition of the great arteries; TOF, Tetralogy of Fallot; VSD, ventricular septal defect.

of patients (80%), the VT was macro-re-entrant. As stated above, if the anatomical location of the VT critical isthmus site is identified within an anatomical isthmus, the anatomical isthmus is transected with a linear RF lesion and checked for bidirectional block. So far, the published studies concerning RFCA of VT in TOF are small with limited follow-up, especially the studies targeting fast VT. Therefore, larger studies with longer follow-up are desirable.

AIM AND OUTLINE OF THESIS

The aim of this thesis is to improve the understanding of the VT substrate in TOF, and subsequently improve VT risk stratification and invasive treatment of VT. In **chapter two**, in a cohort of 74 TOF patients who are considered at risk for VT, the properties of the anatomical isthmuses (i.e. width, length and conduction velocity) are determined by electroanatomical mapping during sinus rhythm. The properties of the anatomical isthmuses related to VT are compared to anatomical isthmuses of patients without VT in order to identify isthmus characteristics that can be used for individualized risk stratification and preventive ablation. **Chapter three** describes the acute and long-term outcome of RFCA of anatomical isthmus related VT in a large group of 32 patients with repaired congenital heart disease, predominantly TOF. RFCA in this group was performed using substrate mapping and bidirectional block of the anatomical isthmus that contains the critical VT re-entry circuit site as a procedural endpoint. In TOF, anatomical isthmus related VT of the septal anatomical isthmuses cannot always be successfully ablated via a right-sided approach, and sometimes a left-sided approach is required. The prevalence, the reasons for right-sided failure and

anatomical considerations when performing a left-sided approach are discussed in **chapter four**. **Chapter five** describes the contribution of the VT substrate to QRS duration according to absence/presence of right bundle branch block in a cohort of 78 TOF patients. The **final chapter (chapter 6)** reports the influence of the repair itself, mode of repair and timing of repair on isthmus presence and dimensions in a cohort of 142 TOF post-mortem specimens.

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Arrhythmogenic Anatomical Isthmuses Identified by Electroanatomical Mapping are the Substrate for Ventricular Tachycardia in Repaired Tetralogy of Fallot

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ABSTRACT

Aims

2

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 RV electroanatomical voltage and activation mapping during sinus rhythm 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 versus 16 ± 7 mm, $p=0.001$), narrower (20 ± 8 versus 28 ± 11 mm, $p<0.001$) and had lower CVi (0.36 ± 0.34 versus 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, 87/89 AI of the 46 patients without VT had CVi ≥ 0.5 m/s. Sixty-two patients were discharged without the presence of a SCAI (44 had no SCAI at baseline, 18 underwent ablation of the SCAI) and 10 still had a 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 sinus rhythm are the dominant substrate for VT allowing individualized risk stratification and preventive ablation.

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 to 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 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 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 ≥ 180 ms, non-sustained VT on Holter, at least moderate dysfunction of the left ventricle (LV) or right ventricle (RV), late repair (≥ 5 years of age) and presence of a transannular patch (TA-patch).¹³⁻¹⁹ All patients were treated according to our standard clinical protocol (supplement 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 ECGs, Holter recordings or ICD interrogation. Non-paced 12-lead electrocardiograms (ECGs) were analyzed for QRS duration. Transthoracic

echocardiographic and cardiac magnetic resonance (CMR) imaging studies were reviewed for assessment of biventricular function.

Electrophysiological evaluation consisted of programmed electrical stimulation (PES) to induce VT and detailed 3D-electroanatomical mapping (EAM) during sinus rhythm. All patients were treated according to the standard clinical protocol and provided informed consent.

After venous puncture PES was performed using 3 drive CL (600, 500 and 400ms) with up to 3 extrastimuli (down to 200ms or refractory period) and rapid pacing from at least 2 consecutive RV sites, one close to the infundibular septum before and during isoproterenol infusion (2-10 micrograms/min). EAM (Thermocool catheter; Biosense Webster, Inc, Diamond Bar, CA) could be performed using the same venous access (using the QRS as reference for substrate mapping during sinus rhythm 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 (<1.5mV), pacing was performed with high output (10-mA/2ms). Sites with pacing threshold >10mA were considered unexcitable tissue due to surgical scars and patch material which together with valve annuli can form the boundaries of 4 potential anatomical isthmuses (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 ($\geq 1.5\text{mV}$) could be continuously recorded throughout the anatomical isthmus connecting to normal voltage areas. For each anatomical isthmus width (shortest distance between unexcitable boundaries) and length (distance between the first normal bipolar electrogram at each side of the anatomical isthmus, 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™/CARTO 3™). The fill threshold for EAM of the anatomical isthmuses was set at $\leq 10\text{mm}$ 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 sinus rhythm was defined as the difference between the local activation time at isthmus entrance and exit (figure 1B-C). The conduction velocity index (CVi) was calculated (length/conduction time). Examples of electroanatomical mapping data are provided in figure 2.

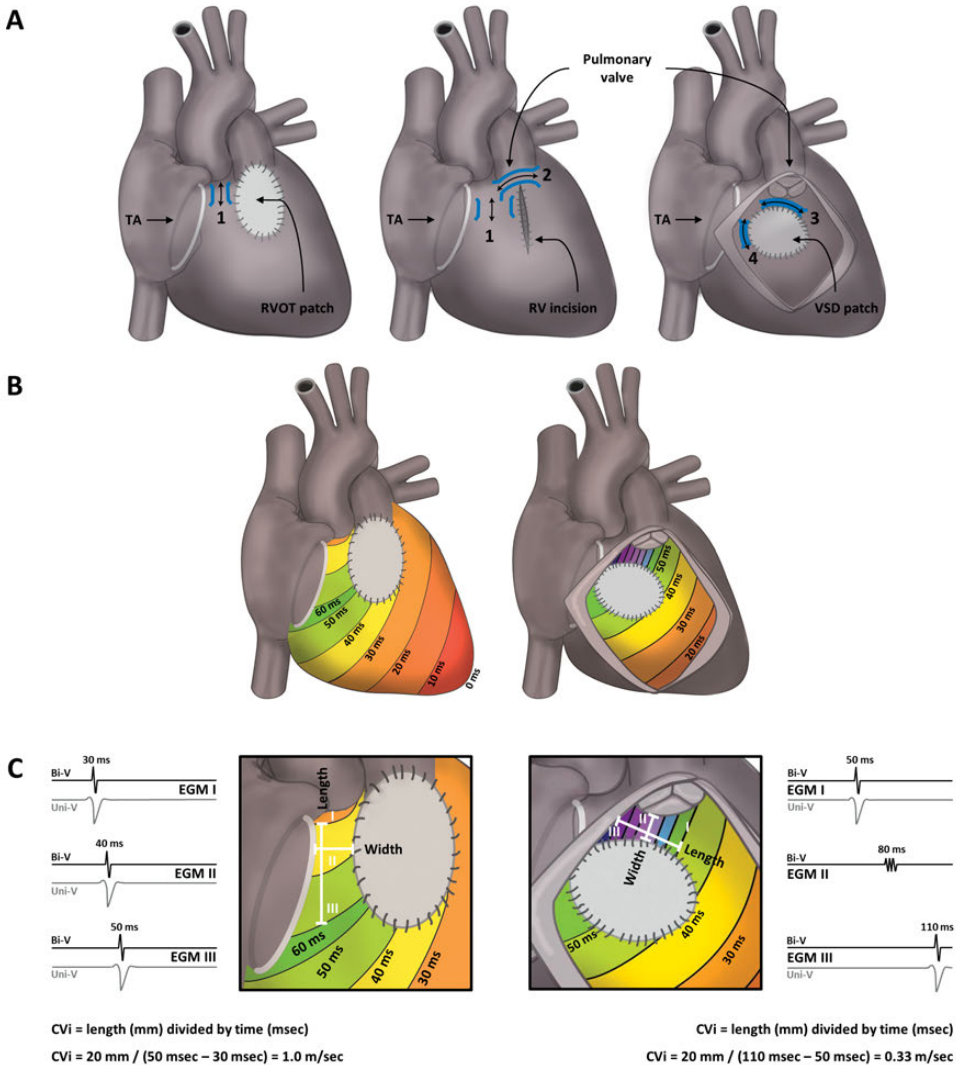


Figure 1. Panel A: Schematic overview of the 4 potential anatomical isthmuses (blue brackets), isthmus 1 bordered by tricuspid annulus (TA) and right ventricular outflow tract patch/right ventricular incision, isthmus 2 by right ventricular incision and pulmonary valve (PV), isthmus 3 by PV and VSD-patch, isthmus 4 by VSD-patch and TA. Panel B: Schematic activation of the right ventricle during SR displayed as colour coded isochronal (10ms) map from red (early activation) to purple (latest activation). Panel 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 (CVi) calculated as indicated. EGM, electrogram; RVOT, right ventricular outflow tract; RV, right ventricular; VSD, ventricular septal defect.

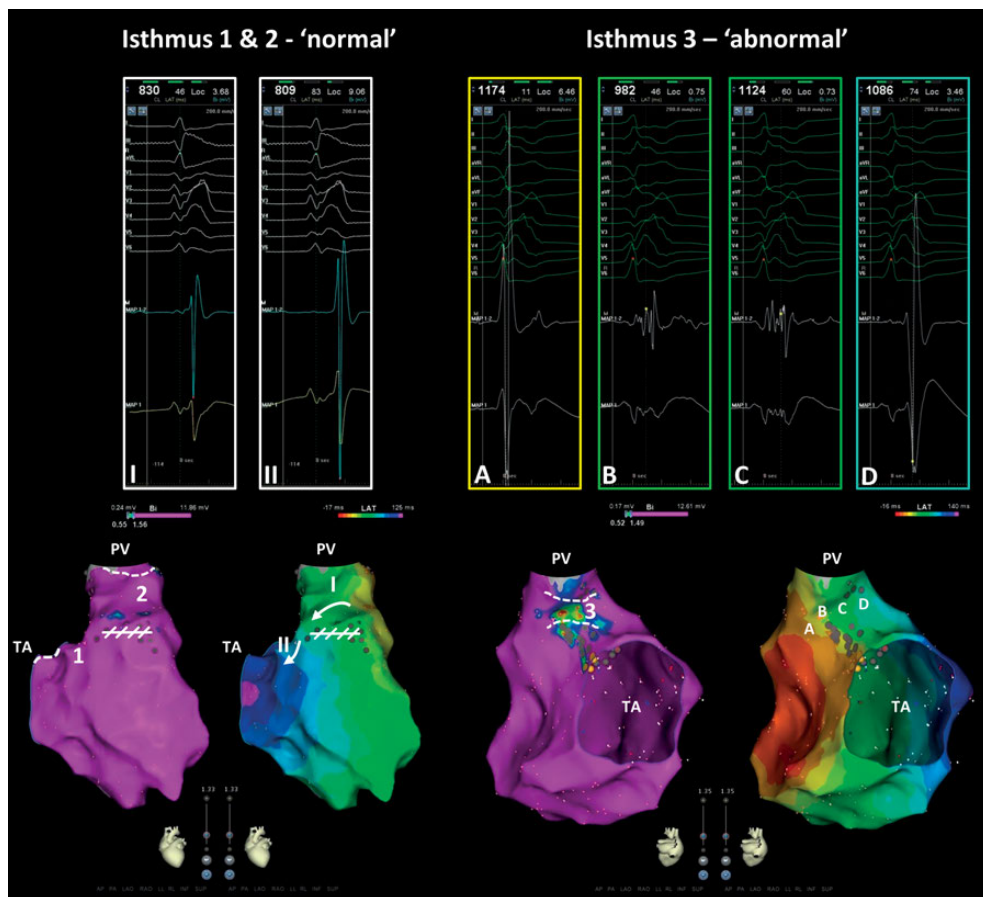


Figure 2. Electroanatomical assessment of anatomical isthmus 1 (between tricuspid annulus (TA) and right ventricular (RV) incision), isthmus 2 (between RV-incision and pulmonary valve) and isthmus 3 (between pulmonary valve (PV) and VSD-patch). On the left, an example of electroanatomical normal isthmuses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

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 (PVCs).

For each induced VT the critical part of the VT re-entry circuit and its spatial relationship to the identified anatomical isthmus was determined by either pace-mapping (at 2mA/2ms up to 10mA/2ms 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 anatomical isthmus 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 anatomical isthmus 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 inter quartile range (IQR) or mean $\pm$ standard deviation (SD) according to data distribution. Categorical data are presented as percentage or frequencies. Differences between the 3 groups were assessed by 1-way ANOVA with post-hoc testing, Kruskal-Wallis and Chi-Square test where appropriate. The properties of VT related anatomical isthmuses and anatomical isthmuses of patients without VT were compared using a Chi-Square 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 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 had one, 29 (39%) two, and 17 (23%) ≥ 3 risk factors for VT; thirteen 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 252msec (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 anatomical isthmus could be identified during SR (69 ± 14 bpm) in 70 patients or RV-pacing in 4 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

Table 1. Baseline Characteristics

Characteristics	No VT (n=46)	VT inducible (n=15)	VT spontaneous & inducible (n=13)	Overall p
Age, y	35.1 ± 14.7	42.8 ± 12.4	$52.3 \pm 14.8^*$	0.001
Male, n (%)	28 (61%)	10 (67%)	9 (69%)	0.824
Age at repair, y	5.3 (2.0–6.9)	5.5 (1.7–16.3)	13.4 (5.8–19.8)*	0.005
Age at repair ≥ 5 y	25 (54%)	9 (60%)	11 (85%)	0.142
TA-patch	19/39 (49%)	7 (47%)	5/11 (46%)	0.978
Time after repair, y	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, y	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; y, year. * $P < 0.01$ vs controls.

Table 2. Presence and characteristics of anatomical isthmuses according to VT profile

Characteristics	No VT (n=46)	VT inducible (n=15)	VT spontaneous & 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/sec	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 VT.

compared to anatomical isthmuses 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 versus 0.78 ± 0.24 , $p<0.001$). Notably, there was no significant difference in isthmus length, width and conduction 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 is provided in supplemental B1). Detailed data for each anatomical isthmus is provided in supplemental B2. No mapping related complications occurred.

Conduction velocity index in controls

CVi 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/s) 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.

Characteristics of VT related anatomical isthmuses

Thirty-seven of 41 induced VTs were related to an anatomical isthmus; twenty-four 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 anatomical isthmus and four patients had 2 VT related anatomical isthmuses each supporting different VT re-entry circuits. VT related anatomical isthmuses were significantly longer and tended to be narrower than isthmuses in patients without VT (figure 3). All VT related anatomical isthmuses were electroanatomical abnormal and slow conducting with a CVi of <0.5 m/s (slow conducting or arrhythmogenic anatomical isthmus). Such a slow conducting anatomical isthmus (SCAI) was only found in 2 patients of group 1.

Four VTs in 4 patients could not be related to an anatomical isthmus. In two patients, both with advanced heart failure and poor RV function and no SCAI, the VT substrate was related

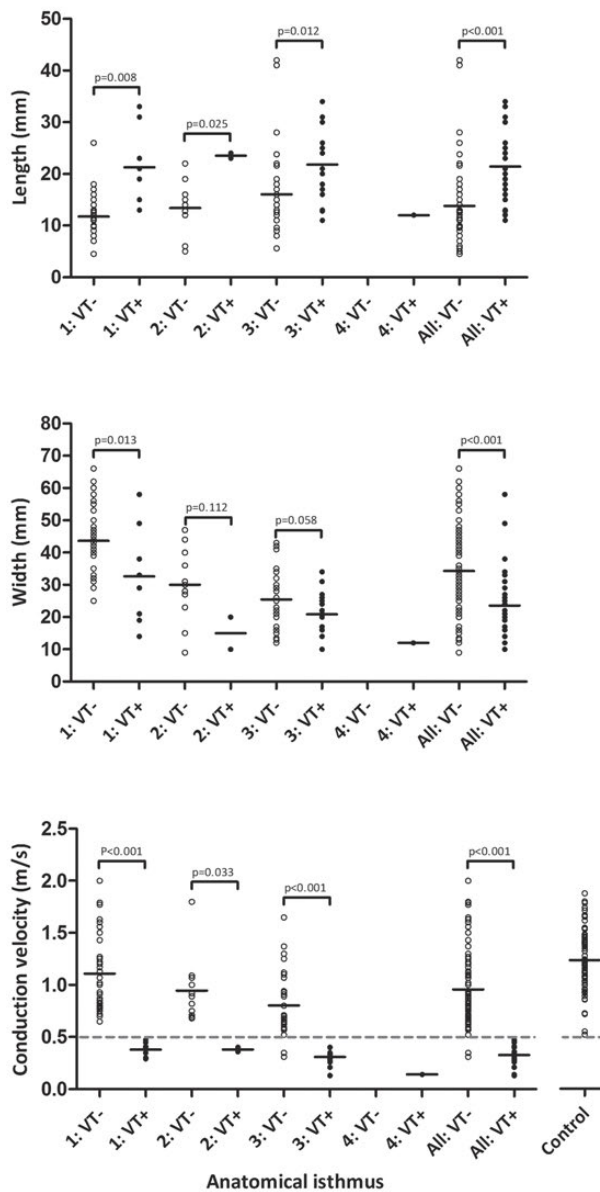


Figure 3. Aligned dot plot. CVi, conduction velocity index; number 1-4 indicate anatomical isthmus 1-4; VT, ventricular tachycardia; VT-, isthmus not critical for VT; VT+, isthmus critical for VT

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 a slow conducting AI (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 anatomical isthmus. In multivariable analyses, none of the variables remained associated with a SCAI. Additional information is provided in table 3.

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 anatomical isthmus 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 2 patients with heart failure and inducible VT that were not related to an anatomical isthmus (group C) underwent ablation, which was successful in one. Eighteen patients (49 ± 14 years, 72% male) received an ICD before discharge; in 6 patients VT-ablation has failed and was not performed in 2. In additional 6 patients an ICD was implanted despite procedural success because of a depressed cardiac function ($n=2$) or patients preference. The remaining 4 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 out of ten 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 group A and B was

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 $\uparrow$	1.07 (1.00-1.15)	0.037
Time after repair, per year $\uparrow$	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.

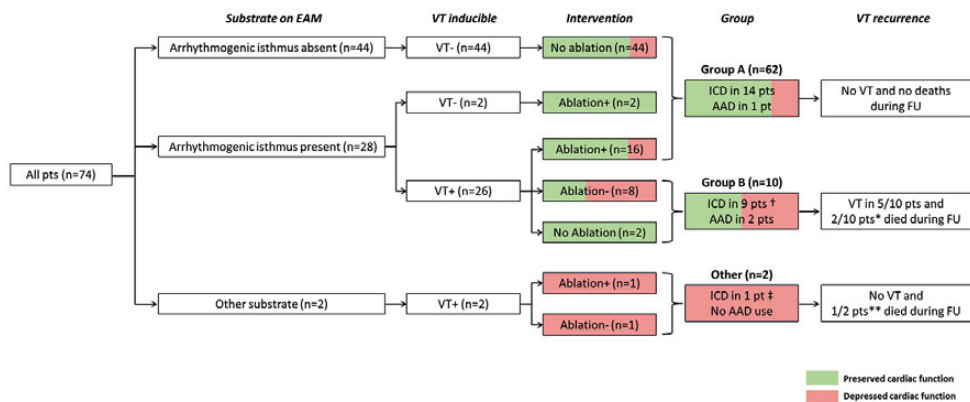


Figure 4. AAD, antiarrhythmic drugs; FU, follow-up; ICD, internal cardiac defibrillator; Pt(s), patient(s); Ablation+, complete successful ablation; Ablation-, no complete successful ablation; VT, ventricular tachycardia; †, no ICD because of physician preference; ‡, no ICD because of mental disability;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

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 anatomical isthmuses ($< 0.5\text{m/s}$) were the substrate for all documented and induced ventricular tachycardia 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 anatomical isthmus 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 msec (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, anatomical isthmuses 1 and 3 were the most prevalent anatomical isthmuses. Isthmus 3 was the narrowest isthmus, which is in line with the observation in postmortem specimen of rTOF.²¹ Of interest, anatomical isthmus 3 as compared to 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 anatomical isthmus are the key determinants for VT. All VT related anatomical isthmuses 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 to 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 anatomical isthmuses 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 two years of life. Of importance, despite early repair, isthmus 3 was slow conducting in 5 (33%) and related to VT in 4 (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 intraoperatively for those who require a second surgical interventions for pulmonary valve replacement. 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 electroanatomical mapping 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 anatomical isthmuses may not change during follow-up. Wider anatomical isthmuses 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 anatomical isthmuses are the dominant substrate for VT and can be identified by electroanatomical mapping via a single venous access allowing individualized risk stratification and tailored treatment.

ACKNOWLEDGMENTS

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

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SUPPLEMENT A

Clinical protocol

Electrophysiological evaluation of patients with repaired Tetralogy of Fallot with documented ventricular arrhythmias (VA) or considered at risk for VA referred to the Electrophysiology service for diagnostic testing, risk stratification or treatment.

2

1. Background

Tetralogy of Fallot (TOF) is associated with late morbidity and mortality due to ventricular arrhythmias (VA).^{1, 2} The majority of VA are sustained monomorphic ventricular tachycardias (MSVT).³ These VTs are often fast and require ICD shocks in patients who have received an ICD for primary or secondary prevention.³ In patients without ICDs fast VTs may be fatal even in the presence of a preserved RV and LV function. Of concern, two thirds of repaired TOF (rTOF) patients who died suddenly or have experienced a life threatening VT had a preserved biventricular function before the first event.^{4, 5} It is therefore of utmost importance to identify patients at risk for VT and sudden cardiac death (SCD). Several risk factors (RF) have been identified associated with VT and/or SCD, however with limited predictive value.

Reported RF include: syncope, QRS duration ≥ 180 ms, non-sustained VT on Holter, at least moderate dysfunction of the left ventricle (LV) or right ventricle (RV), late repair (≥ 5 years of age), presence of a transannular patch (TA-patch) and extensive ventricular fibrosis on (CE)-CMR.⁶⁻¹³

Prophylactic implantation of ICDs is still under debate. According to current guidelines, primary prevention ICD implantation is considered reasonable in selected adults with rTOF and multiple risk factors for SCD, such as left ventricular systolic or diastolic dysfunction, nonsustained VT, a QRS duration greater than 180ms, extensive right ventricular scarring, or inducible sustained VT at electrophysiological study.¹⁴ If symptoms of presyncope or syncope are reported, an induction protocol for both VT and supraventricular tachycardias is considered to be helpful. However, not all rTOF patients that experience VT during follow-up and had undergone programmed electrical stimulation prior to ICD implantation have been inducible in the EP lab.¹⁵ These data suggest that programmed electrical stimulation alone may not be sufficient to proof the presence of a substrate for VT in all patients.

The majority of VT in rTOF is due to macroreentry with critical VT isthmus sites located within anatomically defined regions.¹⁶ These anatomical isthmuses can be identified during stable sinus rhythm facilitated by 2D electroanatomical mapping systems and immediately targeted by radiofrequency catheter ablation in the lab or by surgical ablation in those who are considered for re-operation.¹⁷ In prior mapping and ablation studies it has been demonstrated that VT related anatomical isthmuses often show characteristics consistent with slow conduction, which is an important pre-condition for reentry VT. In a series of adults with repaired congenital heart disease (majority rTOF) who underwent VT ablation, complete procedural success has been defined as non-inducibility of any VT and transection of the critical anatomical isthmus.¹⁷ This endpoint was achieved in 74% and

none of the patients in whom complete procedural success was achieved had recurrence of a monomorphic VT during long term follow-up. These data further support the strong link between “arrhythmogenic” anatomical isthmuses and macroreentrant VTs. Although almost all rTOF patients have anatomically defined isthmuses, not all are related to VT or may serve as a potential substrate for VT.

To improve both risk stratification and identification of the potential VT substrate in an individual patient with rTOF with VT or who is considered at risk for VA, programmed electrical stimulation *and* right ventricular electroanatomical mapping has been included in our routine clinical protocol for risk assessment in patients after repair of TOF.

2. Patients eligible for the protocol

All rTOF patients who are referred for electrophysiological evaluation and/or for treatment of ventricular arrhythmias, who had documented VT or who are considered at risk for VT. Other eligible patients for the protocol are pre-operative patients prior to pulmonary valve replacement.

After complete non-invasive evaluation (ECG, Holter, exercise test, imaging studies (echocardiogram, contrast enhanced (CE)-MRI) on the discretion of the referring GUCH cardiologist), all eligible patients are presented and discussed during our weekly conference in the presence of GUCH cardiologist, Electrophysiologist and Congenital surgeon. Repaired TOF patients are considered at risk when at least one of the following risk factors is present:⁶⁻¹³

- I. (Pre)Syncope
- II. QRS duration $\geq 180\text{ms}$
- III. Non-sustained VT on Holter
- IV. Moderate dysfunction of the left ventricle
- V. Moderate dysfunction of the right ventricle
- VI. Late repair (≥ 5 years of age)
- VII. Presence of a transannular patch
- VIII. Extensive ventricular fibrosis on (CE)-CMR

3. Electrophysiological evaluation and ablation

All patients are informed in advance regarding the potential outcome of the electrophysiological evaluation and the potential treatment options (catheter ablation, ICD implantation, surgical ablation, if appropriate). All patients have to provide oral informed consent prior to the procedure, which is documented in the medical chart.

VT induction and electroanatomical mapping

Programmed ventricular stimulation and electroanatomical right ventricular mapping (EAM) are performed in a non-sedated and post absorptive state using a single venous sheath (8 French, modified Seldinger Technique). Heparine bolus is administered via

the venous sheath and heparine is administrated during the procedure to maintain an ACT 250-300. A quadripolar catheter is inserted in the RV to perform standard programmed electrical stimulation (PES). PES consists of three drive cycle lengths (600, 500 and 400ms) with up to 3 ventricular extrastimuli ($CL \geq 200ms$) and burstpacing, from the RV apex and the RVOT which will be repeated with isoprotenerol (2-10 μ g/min) if necessary. Electroanatomical voltage and activation mapping is performed during sinus rhythm (SR) or RV pacing in patients who are pacemaker dependent using a non-fluoroscopic 3D mapping system using a single venous access. Surface QRS is used as reference for substrate mapping during SR. An electroanatomical reconstruction of all anatomical isthmuses is obtained by identification of the anatomical border as previously described.^{16, 17} After completion of the voltage and activation maps characteristics of each anatomical isthmus are assessed (electrograms characteristics, activation sequence consistent with conduction delay) to identify those anatomical isthmuses likely related to VT.

Patients inducible for MSVT

For each induced VT the critical part of the VT re-entry circuit and its spatial relationship to the identified anatomical isthmus is determined by either pace-mapping (at 2mA/2ms up to 10mA/2ms 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 is indicated.

Patients inducible for MSVT related to an anatomical isthmus

After VT mapping and after the identification of an anatomical isthmus related to VT, ablation will be offered and performed during the same procedure (as discussed with the patient before the procedure). Before ablation, a second venous access has to be obtained for a steerable quadripolar RV catheter allowing for pacing at both sides of the targeted anatomical isthmus. Endpoint of RF ablation is defined as non-inducibility of VT and bidirectional isthmus conduction block.

Patients inducible for MSVT or patients not inducible for MSVT but with abnormal anatomical isthmuses (slow conduction) during sinus rhythm scheduled for re-operation

In patients in whom pulmonary valve replacement is recommended intraoperative cryoablation of the VT related anatomical isthmus will be performed. Preventive ablation of a potentially arrhythmogenic isthmus will be considered and discussed with the patient.

Post-procedural protocol

The venous sheath(s) is(are) removed in the cathlab. Routine control of the vascular access site is performed in the lab and 4 hours later on the ward. All patients who underwent ablation receive an echocardiogram the next day before discharge. If patients meet the ESC CHD-guidelines for ICD-implantation after the procedure, an ICD will be offered.¹⁴

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SUPPLEMENT B: RESULTS

Supplement B1. Association between age and the conduction velocity index of the slowest anatomical isthmus

	Conduction velocity, m/s odds ratio (95%, CI)	p
VT+		
Age, per year ↑	-0.001 (-0.010 – 0.009)	0.901
VT-		
Age, per year ↑	-0.003 (-0.008 – 0.002)	0.271
Control group		
Age, per year ↑	-0.006 (-0.015 – 0.004)	0.196

CI; confidence interval; VT, ventricular tachycardia; VT-, no spontaneous/inducible VT; VT+, spontaneous and/or inducible VT.

Supplement B2. Presence and characteristics of anatomical isthmuses according to VT profile

Characteristics	No VT (n=46)	VT inducible (n=15)	VT spontaneous & inducible (n=13)	Overall p
Isthmus 1	40 (87%)	14 (93%)	13 (100%)	0.335
EA abnormal	0	3**	6**	<0.001
Width (mm)	44±10	37±8	35±14	0.017
Length (mm)	12±4	13±6	18±8**	0.003
CVi (m/sec)	1.11±0.34	0.90±0.48	0.69±0.32**	0.002
Isthmus 2	11 (24%)	4 (27%)	4 (31%)	0.878
EA abnormal	0	1	4** †	0.001
Width (mm)	30±12	25±14	25±10	0.648
Length (mm)	13±5	17±8	27±3**	0.004
CVi (m/sec)	0.95±0.32	0.78±0.27	0.40±0.09*	0.015
Isthmus 3	38 (83%)	13 (87%)	13 (100%)	0.269
EA abnormal	5	11**	12**	<0.001
Width (mm)	26±8	21±6	20±6	0.043
Length (mm)	16±8	20±7	20±7	0.101
CVi (m/sec)	0.80±0.29	0.40±0.21**	0.29±0.14**	<0.001
Isthmus 4	0 (0%)	4 (27%)**	0 (0%) †	<0.001
EA abnormal		2		
Width (mm)		19±5		
Length (mm)		16±7		
CVi (m/sec)		0.72±0.67		

CVi, conduction velocity index; EA, electroanatomical; Pts, patients; SMVT, sustained monomorphic ventricular tachycardia; *, P<0.05 vs SMVT-; **, P<0.01 vs SMVT-; †, P<0.05 vs SMVT inducible.



Reentry Using Anatomically Determined Isthmuses: a Curable Ventricular Tachycardia in Repaired Congenital Heart Disease

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ABSTRACT

Background

Ventricular tachycardia (VT) is an important cause of late morbidity and mortality in repaired congenital heart disease (rCHD). The substrate often includes anatomical isthmuses that can be transected by radiofrequency catheter ablation (RFCA) similar to isthmus block for atrial flutter. This study evaluates the long-term efficacy of isthmus block for treatment of reentry VT in adults with rCHD.

Methods and Results

Thirty-four patients (49 ± 13 years, 74% male) with rCHD who underwent RFCA of VT in two centres were included. Twenty-two (65%) had a preserved left and right ventricular function. Patients were inducible for 1 (IQR 1-2) VT, median cycle length 295ms (IQR 242-346). Ablation aimed to transect anatomical isthmuses containing VT reentry circuit isthmuses. Procedural success was defined as non-inducibility of any VT *and* transection of the anatomical isthmus and was achieved in 25 (74%) patients. During long-term follow-up (46 ± 29 months) all patients with procedural success (18/25 with ICDs) were free of VT recurrence but 7/18 experienced ICD related complications. One patient with procedural success and depressed cardiac function received an ICD shock for VF. None of the 18 patients (12/18 with ICDs) with complete success *and* preserved cardiac function experienced *any* ventricular arrhythmia. In contrast, VT recurred in 4/9 patients without procedural success. Four patients died from non-arrhythmic causes.

Conclusions

In patients with rCHD with preserved ventricular function and isthmus dependent reentry, VT isthmus ablation can be curative.

INTRODUCTION

The population of adults with repaired congenital heart disease (rCHD) is growing as improved surgical techniques are extending survival.¹ However, rCHD is still associated with late morbidity and mortality due to ventricular arrhythmias (VA).^{2,3} Ventricular arrhythmias encompass polymorphic ventricular tachycardia (PVT), ventricular fibrillation (VF) and monomorphic ventricular tachycardia (MVT) with potentially different underlying substrates requiring different treatment strategies. Patients who experience any VA are considered candidates for internal cardiac defibrillator (ICD) implantation for prevention of sudden cardiac death (SCD).⁴ ICDs, however do not prevent VA and are frequently associated with device related complications and inappropriate therapy in rCHD.⁵⁻⁷ An important option to prevent MVT is radiofrequency catheter ablation (RFCA)^{8,9}, which may be considered as alternative to ICDs in patients with an *otherwise* low risk for SCD.¹⁰ In scar-related VTs, non-inducibility has often been used as procedure endpoint, and has not been a reliable predictor of freedom from VT during follow-up.¹¹ MVT in adults with rCHD often depends on well-defined anatomical isthmuses.^{8,9} These isthmuses can be transected by RFCA and demonstration of conduction block provides a defined procedural endpoint similar to that for achieving block in the common right atrial flutter isthmus. We hypothesized that this isthmus ablation approach may be sufficiently reliable for ablation to be considered as sole therapy for selected patients with VT due to rCHD.⁹ The aims of the current study were (I) to evaluate the acute and long-term efficacy of isthmus ablation for treatment of VT in a large population of adults with rCHD and (II) to identify patients in whom RFCA may be an alternative to ICD therapy.

METHODS

Patient Population

The series consisted of consecutive patients with rCHD, who underwent RFCA of VT aiming to target anatomical isthmuses in two centers (Brigham and Women's Hospital, Leiden University Medical Center) between 2001 and 2012. The medical records of all patients were reviewed for type of malformation, surgical history, device implantation, presenting symptoms, documented arrhythmias and medication at referral. Non-paced 12-lead ECGs recorded at admission were analyzed for QRS duration. The occurrence of non-sustained VT (≥ 3 consecutive beats, rate >120 beats/min, lasting <30 s) was captured from Holter recordings. The review of medical records was approved by the hospital human subject protection committee. Nine patients were included in our initial report 7 years ago.⁹

Hemodynamic evaluation before ablation

Echocardiographic and cardiac magnetic resonance imaging (CMR) studies performed prior to ablation were collected. The echocardiographic studies were reviewed by an independent imaging cardiologist (E.H.) experienced in CHD and blinded to outcome. RV systolic function

was semi-quantitatively assessed and classified as poor, moderately reduced, mildly reduced or good.^{12, 13} Tricuspid annular plane systolic excursion (TAPSE) was measured but not used in case of tricuspid valve annuloplasty. Mildly reduced or good RV function with a TAPSE ≥ 14 mm was considered as preserved. The LV ejection fraction was assessed by Simpson's method and classified as poor ($<30\%$), moderately reduced ($30-39\%$), mildly reduced ($40-54\%$) or good ($\geq 55\%$). LVEF $\geq 40\%$ was considered preserved LV function. If available, cardiac volumes and volume derived parameters were evaluated by CMR. In case of discrepancy CMR results determined the definitive classification. Designation of preserved cardiac function required both preserved RV and LV function.

Electrophysiology Study, Electroanatomical Mapping and Ablation

Programmed electrical stimulation (PES) was performed from the RV apex and RVOT with 3 extra stimuli at 3 basic cycle lengths (CL) including administration of isoproterenol. The method to obtain a 3D reconstruction of all specific anatomic isthmuses and targeting the VT related isthmus by ablation has been previously described in detail.⁹ Briefly, 3D RV and/or LV electroanatomical bipolar voltage mapping during SR or RV pacing was performed using a venous and/or retrograde access. In transposition of the great arteries (TGA), the morphological right ventricle was approached via the aorta in the case of an atrial switch and via venous access in the case of an arterial switch operation. To identify prosthetic material adjacent to normal myocardium and surgical scars high output pacing was performed at all low voltage sites (<1.5 mV). Sites with a pacing threshold >10 mA were tagged as electrically unexcitable scar (EUS).¹⁴

Tricuspid and mitral annulus were identified by atrial and ventricular electrograms of approximately equal amplitudes. Areas of EUS (e.g. incisions, patch material) and valve annuli were considered to be boundaries of anatomical isthmuses. The critical re-entry circuit isthmus of each induced VT was determined by diastolic activity and slowing or termination during RF delivery and/or entrainment during VT and/or by pace-mapping (pace-match $\geq 10/12$ leads).^{9, 14} If the critical isthmus site was located within an anatomically defined isthmus the anatomical isthmus was considered "critical" and the adjoining anatomical boundaries were connected by a linear RF lesion. RF ablation was performed with an open saline-irrigated catheter (power limit, 50W) in 32 patients (Thermocool) or an 8-mm-tip catheter (power limit, 70W) in 2 patients. In all studies high output pacing (10mA, 2ms) along the line was performed and no capture was considered as a transected anatomical isthmus. Block was further supported by the presence of double potentials and/or a change in activation sequence during SR or RV-pacing after ablation (figure 1). More recently differential pacing was performed to confirm bidirectional conduction block. After transection of the anatomical isthmus programmed stimulation was repeated.

Complete procedural success was defined as non-inducibility of any VT *and* transection of the critical anatomical isthmuses; partial success, if only non-clinical VTs could be induced and/or transection of the corresponding anatomical isthmus of the non-clinical VT could not be performed and/or no potential re-entry circuit site for a non-clinical VT

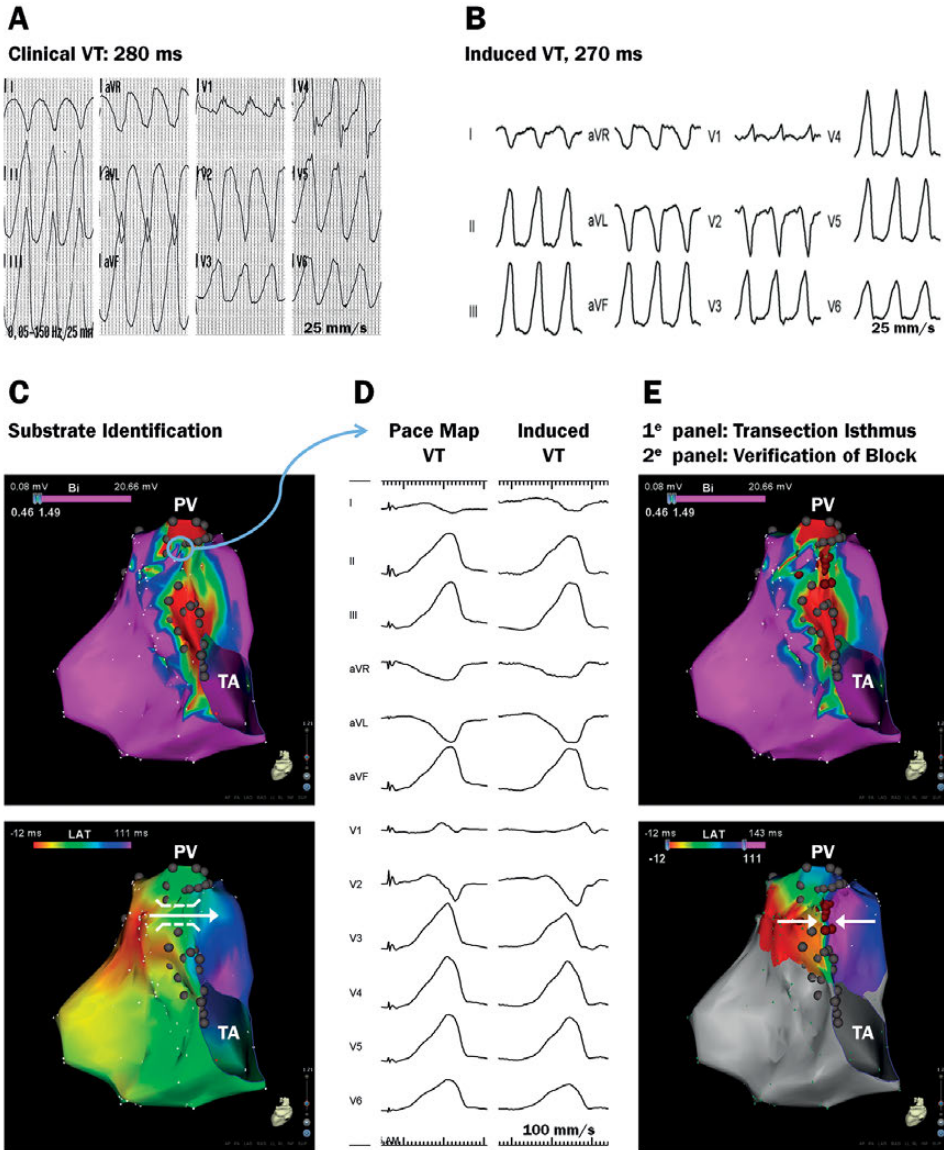


Figure 1. Procedural workflow. Panel A: 12-lead VT-ECG recorded during resuscitation. Panel B: Induced clinical VT. Panel C: Bipolar voltage and activation map during sinus rhythm (modified PA-view). Voltage and activation time is color-coded according to bar, gray tags indicate unexcitable tissue. Anatomical isthmus 3 (white dashed brackets) is present between the VSD-patch and the pulmonary valve (PV) with continuous conduction. Panel D: VT isthmus site within anatomical isthmus 3 is identified by pace-mapping. Panel E: Voltage and activation map after ablation. Red tags indicate ablation sites. After a linear RF lesion through isthmus 3, the activation sequence has changed (white arrows). TA indicates tricuspid annulus.

could be identified; failure, if the clinical or presumed clinical VT remained inducible and/or transection of the corresponding anatomical isthmus could not be performed and/or no potential re-entry circuit site for a clinical VT could be identified. The procedural outcome was considered undetermined if the induction protocol was not repeated after ablation.

3

Follow-up

In patients without an ICD prior to ablation, an ICD was recommended if indicated according to current guidelines.⁴ Anti-arrhythmic drugs (AAD) were discontinued at the discretion of the electrophysiologist. Patients were followed according to the institutional protocol. All episodes of spontaneous sustained VA and appropriate and inappropriate ICD therapy were recorded. VT was considered sustained when ≥ 30 seconds or terminated by the ICD. Recurrence was defined as documented sustained VT and/or symptoms highly suspicious for sustained VA. Device related complications were registered. Mortality was assessed from hospital records. For patients that were not followed at the two institutes' outside records of the clinical and device follow-ups were obtained.

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation (SD) or median with the interquartile range (IQR), according to variable distribution and categorical variables as percentages and frequencies. Patients with and without complete procedural success were compared using Student's t-test, Mann-Whitney U test, Chi-Square test and Log-rank test where appropriate. Odds and hazard ratios of gender, age (at repair), pulmonary valve replacement (PVR), LV function, RV function, cardiac function, number and average VT cycle length (VTCL) of induced VTs were calculated for acute procedural outcome, sustained MVT and VA occurrence during follow-up using univariate logistic regression and hazard's Cox's proportional hazard regression analysis where appropriate. The Kaplan Meier method was used to plot freedom of sustained MVT in patients with and without complete procedural success and freedom of appropriate ICD therapy and inappropriate shocks in patients with complete procedural success and preserved cardiac function. P value of 0.05 was considered significant. SPSS software (20.0 Windows, SPSS Inc, Chicago, IL) was used.

RESULTS

Patient characteristics

The population consisted of 34 adults (25 male, 48.6 $\pm$ 13.2years) with rCHD who had undergone total repair at a median age of 10.0 (IQR, 4.5-18.5) years. Twenty-eight had undergone repair of Tetralogy of Fallot (TOF), 2 of TGA (Mustard baffle in one, arterial switch operation in one), 2 of ventricular septal defect (VSD) with bicuspid aortic valve (bAV) or congenital pulmonary stenosis (cPS), 1 of atrioventricular septal defect (AVSD) and 1 of cPS. In 10 prior palliative shunting had been performed and in 13 patients initial repair was followed by reoperation, which was pulmonary valve replacement (PVR) in 9 at a mean age

of 36 ± 12 years. At referral 14 patients (41%) had an ICD. Twenty-seven patients presented with spontaneous sustained monomorphic VTs (SMVT) documented on ECGs (18) and/or ICDs (14). In the remaining 7 patients SMVT was suspected and could be induced during programmed electrical stimulation. Mean QRS duration (non-paced; $n=29$) was 161 ± 29 msec; in 21% QRS duration exceeded 180 msec.

Hemodynamic characteristics

Echocardiography was performed in 32 patients and 11 had undergone CMR. In 32 patients imaging was performed during admission for RFCA or within the preceding 6 months. In two patients, imaging studies that were acquired >6 months before RFCA and after RFCA showed similar results suggesting stable cardiac function. In only one patient imaging results were discrepant (RV function moderately reduced on echocardiography, but preserved (RVEF 41%) on CMR). RV function was preserved in 71% and LV function in 82% of the patients. Both RV and LV function were preserved in 22 (65%) patients (table 1).

Mapping and ablation outcome

The 34 patients had 61 different VTs (median of 1 (1–2) VT/pt) inducible with a median VTCL of 295ms (IQR 242–346). In all patients with VT documentation the (presumed) clinical VT could be induced. In all 7 patients without prior VT documentation only one VT could be reproducibly induced and was considered the clinical VT. Mapping revealed 6 different anatomical isthmuses (figure 2). In all patients, at least one isthmus could be identified (median of 2 (2–3) isthmus/patient). Isthmus 1 was bordered by the tricuspid annulus (TA) and a previous RV-incision/RVOT-patch and was present in 30 patients; isthmus 2 by a previous RV-incision and the pulmonary valve (PV) and present in 7 patients. Isthmus 3 was bordered by the PV and VSD-patch, present in 30 patients and isthmus 4 was bordered by the VSD-patch and the TA and present in 7 patients.⁹ Isthmus 5 was bordered by the aortic root and a basal septal scar in 1 patient¹⁵ and isthmus 6 was bordered by the mitral annulus and a basal-posterolateral LV scar in 1 patient. In all 34 patients the anatomical isthmus related to the (presumed) clinical VT could be identified. In 10 patients, two or more VTs shared the same anatomical isthmus. Furthermore, nine patients had two anatomical isthmus related to different VTs (additional mapping data is provided in supplemental table A).

Complete procedural success was achieved in 25 patients (21 TOF, 2 D-TGA, 1 VSD and 1 AVSD), partial success in three (2 TOF, 1 VSD) and the procedure failed in four (TOF) patients. Ablation failure or partial success was likely due to the hypertrophy of the targeted anatomical isthmus in three TOF patients and an interposed pulmonary homograft in two TOF patients. In one patient (VSD) RFCA was withheld because of the proximity of the His bundle and in one TOF patient no critical reentry circuit site for two VTs could be identified. In two patients with impaired cardiac function no re-induction was performed (length of the procedure, induced VT that degenerated to VF requiring defibrillation). There was no difference in procedural

Table 1. Baseline and hemodynamic characteristics

Characteristics	
Age (years)	48.6±13.2
Gender (male)	25 (74%)
Presentation	
Sustained monomorphic VT documented	27 (79%)
Sustained monomorphic VT suspected	7 (21%)
Resuscitated	1 (3%)
Syncope	1 (3%)
Palpitations and/or documented non-sustained VT	5 (15%)
Supraventricular Tachycardias	17 (50%)
Atrial flutter	13 (38%)
Atrial fibrillation	9 (27%)
Atrioventricular nodal reentry tachycardia	1 (3%)
Medication at Admission	
Class-I anti-arrhythmic drug	1 (3%)
Class-III anti-arrhythmic drug	11 (32%)
Amiodarone	5 (15%)
Beta-Blocker	16 (47%)
Calcium-Antagonist	1 (3%)
Echocardiography	32 (94%)
TAPSE ≥14 mm (applied in 28/32 pts)	22 (79%)
Right Ventricular Function	
Good	9 (28%)
Mildly Reduced	13 (41%)
Moderately Reduced	6 (19%)
Severely Reduced	4 (13%)
Left Ventricular Function	
Good	13 (41%)
Mildly Reduced	13 (41%)
Moderately Reduced	4 (13%)
Severely Reduced	2 (6%)
MRI	11 (32%)
RVEF≥40%	9 (82%)
LVEF≥40%	11 (100%)
Preserved cardiac function	22 (65%)

PVR, pulmonary valve replacement; TAPSE, tricuspid annular plane systolic excursion; and VT, ventricular tachycardia.

success between rCHD patients with rTOF and without rTOF ($p=0.675$). Cardiac function was preserved in 18 of 25 patients with complete success, in 4 of 7 patients with partial success or procedural failure and in none of the 2 patients with undetermined procedural outcome. On univariable analysis LV function ($p=0.01$) and the number of induced VTs ($p=0.02$) were related to an unsuccessful procedure (table 2).

The average procedure, fluoroscopy and RF time were respectively 221 ± 73 , 46 ± 21 and 22 ± 16 minutes. There was no difference in procedure, fluoroscopy and RF time between

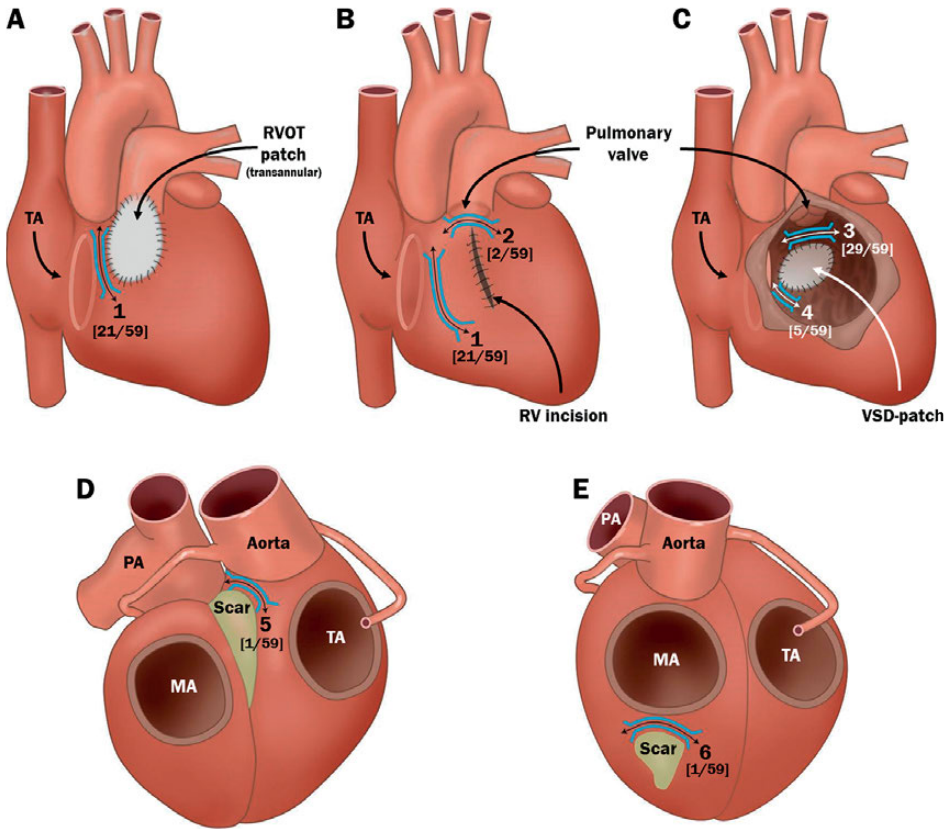


Figure 2. Schematic overview and prevalence of the six identified anatomical isthmuses. A-C previously reported anatomical isthmuses.⁹ Additional isthmuses are illustrated (D, patient 29 (supplement), complex TGA; E, patient 32 (supplement), VSD, bicuspid aortic valve and baso-inferolateral scar). The number of critical VT isthmus (n=59) mapped to anatomical isthmuses is provided (brackets). MA indicates mitral annulus; PA, pulmonary artery; RVOT, right ventricular outflow tract; TA, tricuspid annulus.

patients with and without complete procedural success. Two patients had procedural complications. One patient with poor cardiac function required ICU admission after cardioversion of a hypotensive VT followed by low cardiac output. He fully recovered the following day. One patient had femoral access site bleeding requiring transfusion. There was no procedural related mortality.

Follow-up

Twenty-seven (79%) patients were discharged with an ICD, table 3. Five of the 25 patients with complete success were discharged with antiarrhythmic drugs (amiodarone 1, sotalol 4) because of supraventricular arrhythmias (n=4) and/or presentation with an electrical storm (n=2). Fifteen of the 18 patients with complete procedural success and preserved cardiac function were discharged without any AAD. Four of the 9 patients without complete

Table 2. Univariate predictors of no complete procedural success

Univariate Variables	No Complete Success Odds Ratio (95% CI)	p
Male	1.36 (0.23-8.22)	0.74
Age, per 10 year↑	1.56 (0.83-2.94)	0.17
Age of repair, per 5 year↑	1.25 (0.86-1.82)	0.24
Pulmonary valve replacement (yes)	1.58 (0.30-8.35)	0.59
LV function, per category↓	7.10 (1.62-31.09)	0.01
RV function, per category↓	1.24 (0.58-2.66)	0.58
Impaired cardiac function (yes)	3.21 (0.66-15.58)	0.15
Number of induced VTs	2.33 (1.12-4.86)	0.02
Mean CL of induced VTs, per 10 ms↑	1.04 (0.93-1.16)	0.47

CI, cycle length; LV, left ventricular; RV, right ventricular; VT, ventricular tachycardia.

Table 3. Long-term outcome

	No Complete Success (n=9)	Complete Success (n=25)	p
Follow-up (months)	46±22	46±31	0.994
SMVT	4 (44%)	0 (0%)	<0.001
VF	0 (0%)	1 (4%)	0.527
ICD	9 (100%)	18 (72%)	0.205
Appropriate Therapy	4 (44%)	1 (6%)	0.042
ATP	4 (44%)	0 (0%)	0.007
Shock	2 (22%)	1 (6%)	0.350
Inappropriate Shock	1 (11%)	5 (28%)	0.277
Mortality, all-cause	3 (33%)	1 (4%)	0.025
Mortality, cardiac	2 (22%)	0 (0%)	0.010

SMVT, sustained monomorphic ventricular tachycardia; VF, ventricular fibrillation.

procedural success received AAD (Amiodarone 2, Sotalol 2). During long-term follow-up of 46±28 months all patients with complete procedural success remained free of SMVT recurrence (figure 3). None of the 18 patients with complete success and preserved cardiac function experienced any sustained VA. One patient with complete procedural success but poor cardiac function received an ICD shock for VF. Spontaneous SMVT recurred in 4/9 patients without complete procedural success and were terminated by the ICD. In all four patients, the difference between targeted and spontaneous VTCL was <30msec, suggesting recurrence of the same VT. Four patients died during follow-up, two of heart failure (no complete success), one gastrointestinal carcinoma and one of leukemia

No complete procedural success and decreased LV function (p=0.01) were predictors for SMVT occurrence during follow-up (table 4). No complete procedural success (p=0.02),

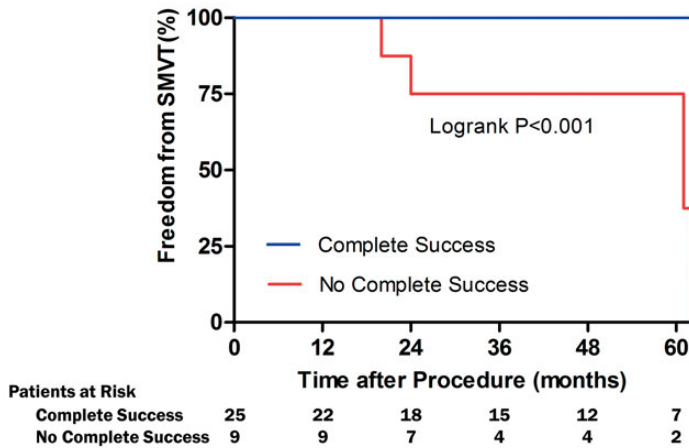


Figure 3. Occurrence of sustained monomorphic ventricular tachycardia (SMVT) during long-term follow-up

Table 4. Univariate predictors for SMVT/VA occurrence during follow-up

Univariate Variables	Any SMVT during FU		Any VA during FU	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Male	0.35 (0.05-2.53)	0.30	0.54 (0.09-3.23)	0.50
Age, per 10 year↑	2.38 (0.97-5.83)	0.06	1.84 (0.88-3.84)	0.11
Age of repair, per 5 year↑	1.25 (0.74-2.11)	0.40	1.25 (0.74-2.11)	0.40
Pulmonary valve replacement (yes)	2.94 (0.41-20.98)	0.28	1.85 (0.31-11.14)	0.50
LV function, per category↓	5.48 (1.45-20.69)	0.01	4.63 (1.60-13.43)	0.01
RV function, per category↓	1.26 (0.48-3.31)	0.64	1.40 (0.61-3.22)	0.43
Impaired cardiac function (yes)	7.02 (0.73-67.90)	0.09	9.43 (1.05-84.98)	0.05
Number of induced VTs	1.42 (0.69-2.93)	0.34	1.31 (0.70-2.45)	0.40
Mean CL of induced VTs, per 10 ms↑	1.03 (0.93-1.14)	0.59	1.04 (0.95-1.14)	0.36
No complete procedural success			13.35 (1.43-124.32)	0.02

CI, cycle length; LV, left ventricular; RV, right ventricular; SMVT, sustained monomorphic ventricular tachycardia; VT, ventricular tachycardia.

impaired LV function ($p=0.01$) and impaired cardiac function ($p=0.05$) were predictors for any VA occurrence (table 4).

ICD related complications

Ten of the 27 ICD recipients experienced ≥ 1 ICD related complications during follow-up: lead fracture ($n=1$), ICD extraction due to infection ($n=4$) and ≥ 1 inappropriate shocks ($n=6$) in response to supraventricular tachycardia ($n=5$) or RV lead over-sensing ($n=1$). Twelve of the 18 patients with complete procedural success and preserved cardiac function were discharged with an ICD and 5 (42%) of them experienced ICD related complications.

DISCUSSION

To the best of our knowledge this is the largest series of VT ablation in patients with rCHD (all available data provided in supplemental table B). Furthermore, ablation was performed with the same systematic approach irrespective of the type of malformation and type of repair, targeting anatomical isthmuses. We found that transection of VT associated anatomical isthmuses by RFCA is feasible in 74% of patients and is highly effective to prevent VT recurrence during long-term follow-up. Of importance, in patients with complete procedural success and preserved cardiac function our findings suggest that this substrate based approach may be considered curative. None of these patients experienced arrhythmias during follow-up ranging from 3 to 128 months, but 42% experienced ICD associated complications. Only 3 were on antiarrhythmic drugs mainly due to supraventricular arrhythmias.

The substrate for fast VT and SCD

Ventricular arrhythmias are an important cause of morbidity and mortality in CHD. In rTOF, monomorphic VT is the most frequently documented VA accounting for >80% of all VA episodes.⁶ The cumulative incidence of sustained VT and SD has been estimated to be 11.9% and 8.3%, respectively at 35 years after repair of TOF and it has been suggested that SD is often due to sustained VT.¹⁶ Of interest, mapping studies performed for both tolerated and hemodynamically intolerated VTs demonstrated that the majority of monomorphic VTs are due to macro re-entry with critical isthmuses located within anatomical isthmuses.^{8, 9} When rapid, these VTs may be fatal even in the presence of a preserved cardiac function. The median VT rate in the current series was 203bpm and for rTOF patients 211bpm, which is similar to the VT rate reported in a recent series of TOF patients receiving ICDs.⁶ Moderate to severe systemic and subpulmonary dysfunction defined as EF<40% has been associated with sudden arrhythmic death in patients with CHD.¹⁷ However, two thirds of patients with CHD that died suddenly had preserved systemic and subpulmonary function, which is comparable to our population.^{17, 18} These findings support the concern that untreated, fast monomorphic VTs is an important cause of SCD when it occurs in CHD with preserved ventricular function.

Outcome of ablation

In our series the substrate of all clinical or presumed clinical VTs was located within an anatomical isthmus and we failed to identify an anatomic isthmus for only 2/61 induced VTs. Repaired TOF constitute the largest subgroup in whom VT ablation is reported and comprised 82% of patients in the current series. However, SMVT related to anatomical isthmuses also occurs in other malformations repaired with surgical scars and patch material, and these can be effectively treated by the same systematic approach. All VT related anatomical isthmuses could be successfully transected in 25 patients resulting in non-inducibility of any VT. None of these 25 patients experienced any monomorphic VT during a mean follow-up of 46

months. This absence of VT is remarkable compared to the 9.8% annual rate of appropriate ICD shocks in TOF patients who receive an ICD after experiencing VA.⁶ This finding supports the hypothesis that the substrate for the fast and monomorphic VTs is indeed confined to the anatomical isthmuses and can be successfully abolished by blocking these isthmuses. The suggested ablation approach may be comparable to isthmus ablation for cavotricuspid isthmus dependent flutter, which also has high acute and long-term success rates. Our findings suggest that isthmus ablation with complete procedural success may be considered curative in patients in whom other ventricular arrhythmia mechanisms are unlikely, and who have preserved cardiac function. These patients had no arrhythmia recurrences and low all-cause and cardiac mortality.

Procedural failure

Procedure failure seemed to have an anatomic basis in 6/9 patients. In three patients the anatomical isthmus (isthmus 1 in 1, isthmus 3 in 2 patients) could not be transected, most likely due to hypertrophied myocardium, despite the use of steerable sheaths and irrigated catheters. In two patients an implanted pulmonary homograft, covering parts of the infundibular septum prevented transection of anatomical isthmus 3. In one patient RFCA was withheld to avoid heart block (isthmus 4). The cumulative incidence of VT recurrence after procedure failure was 100%. Therefore surgical transection of anatomical isthmuses seems a reasonable consideration in those patients that undergo re-operation for pulmonary valve regurgitation and in whom intraoperative ablation can be performed safely. After a failed endocardial approach of a hypertrophied free wall isthmus an epicardial approach may be considered for refractory VTs. However, epicardial access is likely to be hampered by adhesions after prior surgery and should therefore be performed in co-operation with a surgeon.

ICD therapy

The favourable long-term results in patients with procedural success and preserved cardiac function suggest that selected patients may perhaps not benefit from ICD therapy. ICD related complications occurred in 42%, which is in line with prior reports.^{6,7} However, larger studies with longer follow-up are required to exclude that other VA mechanisms may be operative in patients with successful ablation of anatomical isthmus related VT and preserved cardiac function. In patients with impaired LV function ICD implantation is important, as these patients have a significant risk of arrhythmia recurrences.⁶ As in other cardiomyopathies with depressed cardiac function, heart failure related VA mechanisms may be operative. In our series one patient with procedural success for SMVT and depressed cardiac function received an ICD shock for VF. Our results support the current guidelines stating that ICD implantation is not recommended in patients with CHD and spontaneous VT, when the VT can be successfully treated with surgery or RFCA, provided, however, that cardiac function is preserved.¹⁰ Patients discharged without ICD should undergo regular assessment of cardiac function according to the guidelines.

LIMITATIONS

The present study is limited by design and number of patients. Therefore, it is not possible to adjust for confounding in the prediction of acute and long-term outcome. In addition, the results of a case series from two high volume centres may not be translated to other less experienced groups. Testing for bidirectional block of the anatomical isthmus has evolved over time and only in the latter patients pacing manoeuvres were performed. However, no-capture along the line and change of activation sequence as procedural outcome were associated with no VT recurrence and may already be therefore a sufficient endpoint for a linear lesion.

CONCLUSION

In patients with rCHD with preserved left and right ventricular function and anatomical isthmus dependent reentry, VT isthmus ablation can be curative.

ACKNOWLEDGMENTS

We wish to thank R. Slagter for the design of figure 2.

FUNDING SOURCES

Tobias Reichlin has received research grants from the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the Professor Max Cloëtta Foundation and the Uniscientia Foundation Vaduz.

CLINICAL PERSPECTIVE

What is known

- Ventricular arrhythmias (VA) are an important cause of late morbidity and mortality in the growing population of adults with repaired congenital heart disease (rCHD).
- The majority of these VA are fast, monomorphic and thereby life-threatening ventricular tachycardia (VT).
- Small studies have demonstrated that the VT substrate in rCHD often includes anatomical isthmuses that can be transected by radiofrequency catheter ablation (RFCA) with favorable outcome.

What the study adds

- In a large group of rCHD patients, transection of VT associated anatomical isthmuses by RFCA is feasible in 74% of the patients and is highly effective to prevent VT recurrence during long-term follow-up.
- In selected patients with rCHD, with preserved left and right ventricular function, and anatomical isthmus dependent reentry VT in whom other VA mechanisms are unlikely isthmus ablation may be reasonable as sole therapy for the arrhythmia.

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Supplemental table A. Mapping and ablation data

Patient	Gender	Age (years)	CHD	VT inducible (n)	VTCL average (msec)	Isthmus Present (number)	Critical Isthmus (number)	Procedural Outcome
1	Male	55	TOF	4	348	1 and 3	1 and 3	Failure, hypertrophy of isthmus 3
2	Male	40	TOF	1	243	1, 2, 3 and 4	3	CS
3	Male	36	TOF	1	220	3	3	CS
4	Male	58	TOF	2	250	1 and 3	3	CS
5	Male	59	TOF	1	320	1, 2 and 3	1	Failure, hypertrophy of isthmus 1
6	Female	54	TOF	1	318	1 and 3	1	CS
7	Male	53	TOF	1	233	1, 3 and 4	3	CS
8	Male	59	TOF	1	240	1, 2 and 3	1	Undetermined
9	Female	48	TOF	1	386	1 and 4	1	CS
10	Female	35	TOF	1	211	1 and 3	1	CS
11	Male	46	TOF	3	236	1, 2 and 3	1 and 2	CS
12	Male	60	TOF	2	300	1 and 3	1 and 3	CS
13	Female	40	TOF	1	300	1 and 3	3	Failure, pulmonary homograft
14	Female	47	TOF	1	230	1 and 3	3	CS
15	Male	75	TOF	3	279	1 and 2 and 3	1 and 3	CS
16	Female	67	TOF	1	370	1 and 3	3	CS
17	Male	24	TOF	1	240	1, 3 and 4	3	Failure, pulmonary homograft
18	Female	68	TOF	1	270	1 and 3	3	CS
19	Male	40	TOF	2	247	1 and 3	1	CS
20	Male	50	TOF	1	300	1 and 3	1	CS
21	Male	33	TOF	2	255	1, 3 and 4	3 and 4	CS
22	Male	59	TOF	4	397	1 and 3	1 and 3	Partial, hypertrophy of isthmus 3
23	Male	33	TOF	2	290	1 and 3	1	CS
24	Male	45	TOF	2	375	1 and 4	1 and 4	CS
25	Male	52	TOF	6	267	1 and 3	3	Partial, poor induction and pace matches
26	Male	38	TOF	1	290	1 and 3	1	CS

Supplemental table A. (continued)

Patient	Gender	Age (years)	CHD	VT inducible (n)	VTCL average (msec)	Isthmus Present (number)	Critical Isthmus (number)	Procedural Outcome
27	Male	37	TOF	1	345	1 and 3	3	CS
28	Female	59	TOF	2	324	1 and 3	3	CS
29	Male	39	TGA	1	310	5	5	CS
30	Male	22	TGA	1	202	1 and 3	3	CS
31	Male	64	VSD + cPS	5	424	3 and 4	3 and 4	Partial, prevent AV-block (isthmus 4)
32	Male	37	VSD + bAV	1	400	3 and 6	6	CS
33	Male	48	AVSD	1	504	1, 2 and 3	1	CS
34	Female	72	cPS	2	300	1 and 2	1 and 2	Undetermined

AVSD, atrioventricular septal defect; bAV, bicuspid aortic valve; CHD, congenital heart disease; cPS, congenital pulmonary stenosis; CS, Complete procedural success; TGA, transposition of the great arteries; TOF, Tetralogy of Fallot; VSD, ventricular septal defect; VT, ventricular tachycardia; VTCL, VT cycle length.

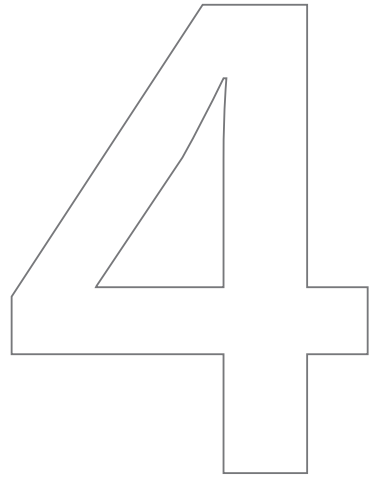
Supplemental table B. Overview of previously published case series and cohort studies on radiofrequency catheter ablation of ventricular tachycardia in repaired CHD

Author Year	Type and number of CHD	Patients (n)	Mean VTCL (ms)	Successful RFCA (n)	AAD after RFCA	Spontaneous VT after RFCA	Follow-up (months)
Case series							
Burton et al. ¹ '93	TOF	2	270 ± 28	2 (100%)	no AAD	0 (0%)	4 ± 3
Horton et al. ² '97	TOF	2	430 ± 71	2 (100%)	not reported	0 (0%)	11 ± 0
Cohort							
Gonska et al. ³ '96	7 TOF, 1 TGA+VSD 1 VSD, 2 PS	11	377 ± 74	9 (82%)	3 Amio, 1 Sot (36%)	1 (9%)	20 ± 9
Morwood et al. ⁴ '04	8 TOF, 3 VSD, 3 miscellaneous (20 procedures)	14	not reported	10 (50%)	not reported	Only successful RFCA reported: 4 (40%)	not reported
Furushima et al. ⁵ '05	4 TOF, 3 DORV	7	346 ± 77	4 (57%)	3 Amio, 3 Sot (86%)	0 (0%)	61 ± 29
Kriebel et al. ⁶ '07	TOF	10	270 ± 40	8 (80%)	not reported	2 (20%)	35 (range 3-52)
Zeppenfeld et al. ⁷ '07	9 TOF, 1 AVSD, 1 TGA+VSD	11	276 ± 78	11 (100%)	2 Amio, 3 Sot (45%)	0 (0%)	30 ± 29

AAD, antiarrhythmic drugs; Amio, amiodarone; AVSD, atrioventricular septal defect; CHD, congenital heart disease; DORV, double outlet right ventricle; PS, pulmonary stenosis; RFCA, radiofrequency catheter ablation; Sot, sotalol; VSD, ventricular septal defect; VT, ventricular tachycardia; TOF, tetralogy of Fallot; TGA, transposition of the great arteries.

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Left-Sided Ablation of Ventricular Tachycardia in Adults with Repaired Tetralogy of Fallot: a Case Series

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ABSTRACT

Background

Radiofrequency catheter ablation (RFCA) of ventricular tachycardia (VT) in repaired Tetralogy of Fallot (rTOF) focuses on isthmuses in the right ventricle but may be hampered by hypertrophied myocardium or prosthetic material. These patients may benefit from ablation at the left side of the ventricular septum.

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Methods and Results

Records from 28 consecutive rTOF patients from two centres, who underwent VT ablation, were reviewed. Ablation targeted anatomical isthmuses containing VT reentry circuits identified by 3D substrate, pace and/or entrainment mapping. A left-sided approach was considered beneficial if (1) right-sided RFCA failed, (2) part of the circuit was mapped to the left side and (3) left-sided RFCA resulted in isthmus transection and prevention of VT induction. In 4/28 patients (52 ± 13 years, 75% male), inducible for 1.5 (quartiles, 1.0 – 2.0) VTs (335 ± 58 msec), left-sided RFCA was performed. In 3 patients RFCA at aortic sites terminated VT related to a septal isthmus and prevented re-induction. In 1 patient, with prior biventricular ICD, diastolic activity was recorded at the left side of the septum in proximity to the His-bundle. RFCA prevented VT re-induction with anticipated complete AV-block. The left-sided approach resulted in complete procedural success (transection of anatomical isthmus and non-inducibility) and freedom of VT recurrence during follow-up (20 ± 15 months) in all patients. Right-sided RFCA failure was likely due to septal hypertrophy in 2, the overlying pulmonary homograft in 1 and overlying VSD patch in 1.

Conclusion

Left-sided RFCA for VTs dependent on septal anatomical isthmuses improves ablation outcome in rTOF.

INTRODUCTION

The population of adults with repaired Tetralogy of Fallot (rTOF) is increasing, as improved surgical techniques are extending survival.¹ Ventricular arrhythmias (VA) are an important reason for late morbidity and mortality.^{1,2} The majority of VA in rTOF are monomorphic VTs.³ The potential re-entry paths causing these VTs are now well described and contain anatomical isthmuses bordered by unexcitable tissue from the tricuspid or pulmonic valve annuli, surgical scars and patch material.⁴ Radiofrequency catheter ablation (RFCA) of the anatomical isthmus causing VT can be highly effective for preventing recurrent VT.⁴ However, achieving conduction block across an isthmus can be difficult due to the hypertrophic myocardium or protection of portions of the isthmus under prosthetic patches or valve homografts. This is particularly true for isthmuses in the outlet septum where the VSD patch is typically located. The aim of this study was to assess the feasibility and utility of ablation from the left ventricle or aorta when ablation from the right ventricle fails. We demonstrate for the first time, to our knowledge, successful ablation of VTs involving the outflow septum using a combined right and left ventricular/aortic root ablation approach.

METHODS

Population

The procedural data of twenty-eight consecutive patients with rTOF, who underwent RFCA of VT in two centres between 2001 and 2013, were reviewed. Patients in whom a left-sided approach was performed were included in the current series. A left-sided approach was considered beneficial if (1) RFCA from the RV failed to prevent VT induction and/or isthmus transection and/or VT recurrence, (2) parts of the VT re-entry circuit isthmus were mapped to the left ventricle (LV) or aortic root and (3) RFCA applied from the left side resulted in isthmus transection and prevented VT induction. The medical records of the patients were reviewed for the surgical history, documentation of spontaneous VT, previous VT ablation and failed drugs. Imaging studies were reviewed for left and right ventricular function at the time of referral. The RV systolic function was semi-quantitatively analysed.^{5,6} The LV ejection fraction was derived by Simpson's method. All patients were treated according to the routine clinical protocol and provided informed consent.

Procedure

The systematic approach for ablation of macro-reentry VT in rTOF has been previously described in detail.⁴ Briefly, the (re-)induction protocol existed of two or three drive cycle lengths (600, 500 and 400 msec) with up to three extra stimuli, burst pacing and isoproterenol from ≥ 2 RV sites (apex and RV outflow tract (RVOT)). A RV bipolar electroanatomical voltage map (EAM) was created using a 3D mapping system (Carto XP/3, Thermocool catheter, Biosense Webster, Inc; Diamond Bar, Calif). At low voltage sites (bipolar recording < 1.5 mV), high output pacing (10 mA at 2-ms pulse width) was performed to identify areas of electrically unexcitable scar/tissue (EUS).⁷ EUS (i.e. VSD-patch, pulmonary homograft, and

previous RV incisions), the pulmonary valve (PV) and the tricuspid annulus (TA) were defined as boundaries of the four previously described anatomical isthmuses in rTOF (for details see figure 1). Two of these anatomical isthmuses (isthmus 3 and 4) involve the septum. The relationship between the critical reentry circuit isthmus of each VT and the anatomical isthmuses was confirmed by concealed entrainment, diastolic activity with VT termination during RF delivery for tolerated VT and/or pace mapping (PM) at sites where QRS morphology matched VT morphology ($\geq 11/12$).⁸ The anatomical isthmus containing the critical VT reentry site was transected with RF current using an open saline-irrigated catheter (power 35-50 W, maximum temperature 45°C) until high output (at least 10 mA, 2 ms pulse width) pacing fails to capture along the ablation line. Block was further supported by the presence of double potentials and/or a change in activation sequence during SR or RV-pacing after ablation. More recently differential pacing was performed to confirm bidirectional conduction block.⁹ After transection of the anatomical isthmus programmed stimulation was repeated.

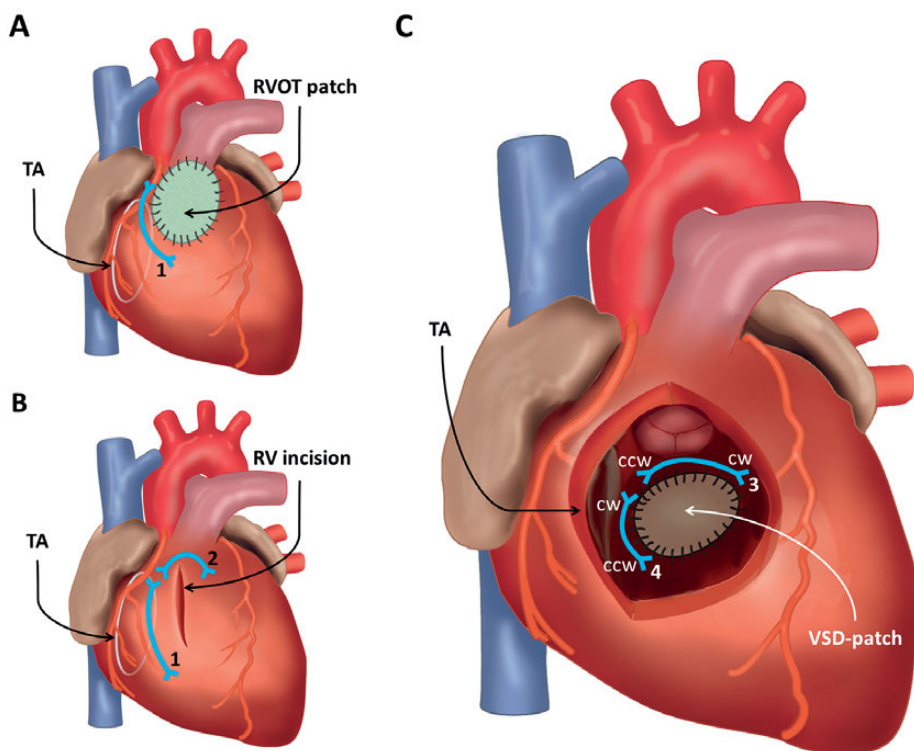


Figure 1. The previously described four anatomical isthmuses for VT in rTOF.⁴ Anatomical isthmus 1 is located between the TA and a RV incision/RVOT patch (panel A, B) and anatomical isthmus 2 is located between a RV incision and PV (panel B). Anatomical isthmus 3, located between the PV and VSD-patch and anatomical isthmus 4, located between the VSD-patch and TA (panel C) are bordering on the septum. Ccw indicates counter clockwise; cw, clockwise; PV, pulmonary valve; rTOF, repaired Tetralogy of Fallot; RV, right ventricle; RVOT, RV outflow tract; TA, tricuspid annulus; VSD, ventricular septal defect; VT, ventricular tachycardia.

Left-sided approach

If VT could not be abolished from the RV and the anatomical isthmus containing reentry circuit sites was in or bordering on the septum, the aorta and LV were mapped using a retrograde approach. The described criteria were applied to confirm that parts of the reentry circuit were located within the same anatomical isthmus but approachable from the left ventricle or aorta. Before RF delivery at aortic sites coronary angiography or aortography was performed to identify the coronary ostia. In the aorta power was limited to a maximal of 35 Watts (figure 2). After RFCA, the induction protocol was repeated.

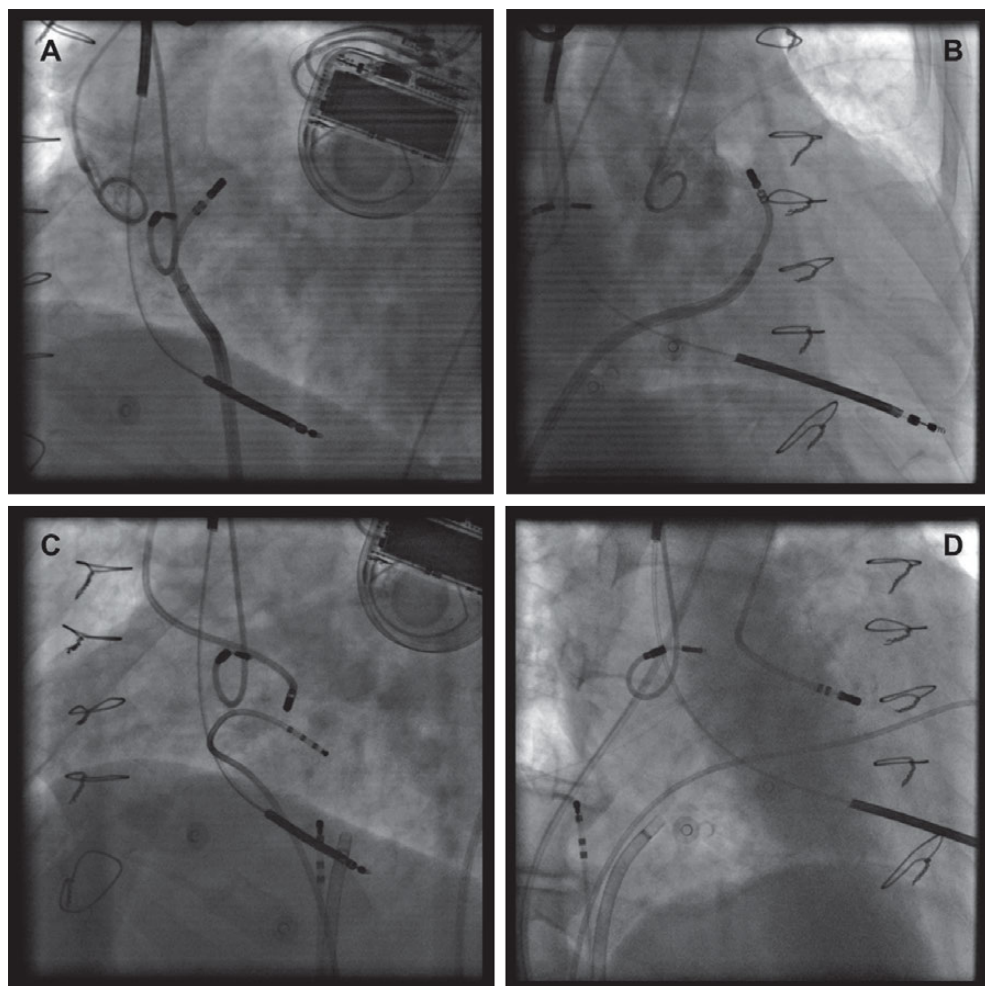


Figure 2. Mapping catheter position on fluoroscopy (case 1). Position of the mapping catheter in the RV during angiography of the aorta in LAO (panel A) and RAO (panel B) view. Position of the mapping catheter in the left coronary cusp of the aorta during VT termination in LAO (panel C) and RAO view (panel D). LAO = left anterior oblique; RAO = right anterior oblique; RV = right ventricle.

Follow-up

In patients without an ICD prior to ablation, an ICD was recommended if indicated according to current guidelines. VA recurrence was defined as documented spontaneous sustained VA and/or symptoms highly suspicious for sustained VA. For patients that were not followed at the two institutes, records of the clinical and device follow-ups including the most recent were obtained.

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Anatomy

In order to gain more insights in the anatomical substrate that may require left-sided RFCA in rTOF, the Leiden collection of malformed hearts was reviewed for rTOF post-mortem specimens. Study of this collection was undertaken in accordance with the local ethics committee and the Dutch regulation for the proper use of human tissue for medical research purposes. Two post-mortem specimens were selected to illustrate (1) the relation between the patch material and the adjacent myocardium and (2) the specific anatomical location and morphology of the infundibular septum.

RESULTS

In 11 of the 28 (39%) consecutive patients with rTOF right-sided RFCA failed to abolish all inducible VTs. In 8 of these 11 patients the VT was mapped to a septal anatomical isthmus (isthmus 3 in 7 pts, isthmus 4 in 1 pt). In four patients a left-sided approach was not taken due to procedural considerations (length of the procedure, poor condition of the patient, inability to re-cross the aortic valve due to position of the aortic root and mild aortic valve stenosis). The presumed reasons for failure of right-sided ablation in these four patients were hypertrophy of the outlet septum in two and a pulmonary homograft in two. In the remaining four patients left-sided mapping and RFCA were performed. These four patients (52 ± 13 years (mean $\pm$ sd), 75% male) were inducible for a median of 1.5 VT (quartiles, 1.0 – 2.0) with a mean VT cycle length of 335 ± 58 msec. Table 1 summarises the baseline characteristics.

Case 1

A 58 year old male had undergone total correction (infundibular resection, transannular patch, patch closure of a perimembranous VSD) at the age of 13 and presented with recurrent, symptomatic, self-terminating broad-complex tachycardias. Echocardiography and MRI revealed severe pulmonary valve regurgitation requiring pulmonary valve replacement (PVR). Before surgery programmed electrical stimulation (PES) and RV EAM were performed. Two fast VTs (cycle lengths 250ms, figure 3) were inducible and substrate mapping identified two anatomical isthmuses: isthmus 1 between the transannular patch and the tricuspid annulus (TA) and isthmus 3 between the pulmonary valve (PV) and the VSD-patch. Both VTs could be mapped to anatomical isthmus 3 with a clockwise activation during VT1 (QR in V1) and counterclockwise activation during VT2 (late transition in precordial lead V_5). As the patient was scheduled for re-surgery, PVR was combined with intraoperative cryoablation

Table 1. Patient characteristics and procedural data.

Patient Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	58	67	45	37
Gender	Male	Female	Male	Male
Prior Shunt	No	No	Yes	No
Age of Repair (years)	13	15	4	3
Type of VSD	Peri-M	Peri-M	Musc	Peri-M
Reoperation	PVR	VSD closure	VSD closure	None
Failed drugs	None	Sotalol	Sotalol Mexiletine	Sotalol
LV ejection fraction	54%	43%	39%	61%
RV function	Moderately Red	Severely Red	Moderately Red	Mildly Red
VT induced (n)	2	1	2	1
Septal isthmus dependent (n)	2	1	1	1
VTCL of induced VT (ms)	245+255	370	370+380	345
Presumed reason right-sided failure	P Homograft	Hypertrophy	VSD-patch	Hypertrophy
Drugs at discharge	None	Sotalol	Sotalol	Nadolol

LV = left ventricular; Peri-M = perimembranous; P homograft = pulmonary homograft; PVR = pulmonary valve replacement; Red = reduced; RV = right ventricular; VSD = ventricular septal defect; VT = ventricular tachycardia; VTCL = VT cycle length.

of isthmus 3. At the postoperatively performed EP study VT1 was again inducible and an ICD was implanted before discharge. Subsequently he had multiple VT episodes terminated by ATP and was intolerant of sotalol. Six months after surgery VT ablation was attempted. Although pacing at isthmus site 3 did not capture, the activation map during sinus rhythm was consistent with continuous conduction through isthmus 3. During VT 1 diastolic activity was recorded at isthmus 3 but RFCA at that region did not terminate VT. These findings suggested that the pulmonary homograft was covering the infundibular septum (figure 4) mimicking scar between the prior pulmonary annulus and the TA. Pacing at the opposite site within the left coronary cusp (LCC, figure 2) captured and resulted in a 12/12 pace-map. During VT mid-diastolic activity was recorded at this site, and RF application terminated VT within 18 seconds and prevented VT re-induction. During 21 months of follow-up the patient had no VT recurrence.

Case 2

A 66 year old female underwent primary repair of TOF at the age of 15 years with resection of severely hypertrophied infundibular muscle, commissurotomy of the PV, partial patch closure of a large perimembranous VSD and suture of a large longitudinal RV incision. Thirteen years later complete closure of the VSD was performed. She subsequently developed recurrent, symptomatic VT terminated by antitachycardia pacing (ATP). During EP study the presumed clinical VT (cycle length 370ms, figure 3) was induced. RV electroanatomic mapping identified

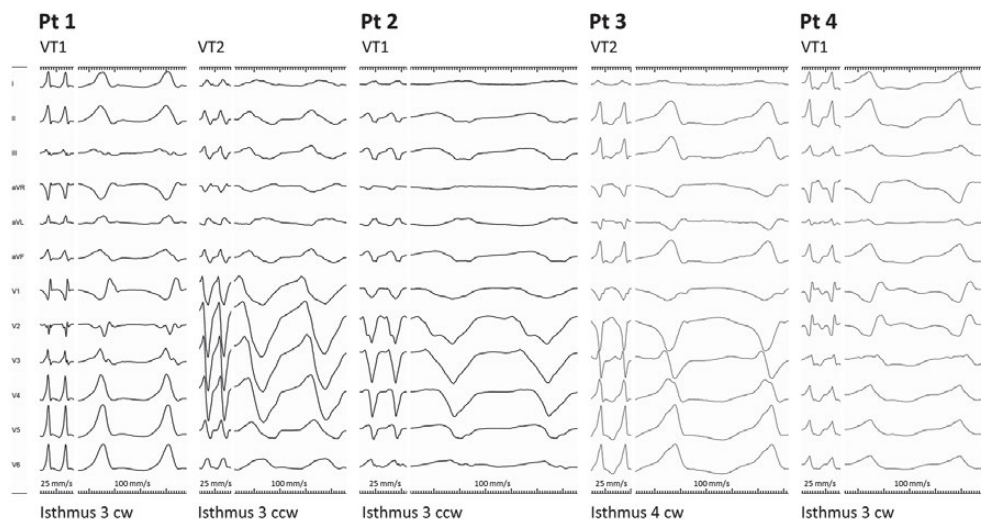


Figure 3. 12 lead ECGs (sweep speed 25mm/s and 100mm/s) of the induced septal VTs in all four cases. In patient one, two and four, the critical reentry site was located at anatomical isthmus 3 (isthmus between VSD-patch and PV). VT1 in patient one and VT1 in patient four demonstrated a clockwise (cw) activation of isthmus 3, please note the QR in lead V1. On the contrary, VT2 in patient one and VT1 in patient two demonstrated a counter clockwise (ccw) activation of isthmus 3, please note the late transition in precordial leads. In patient three, the critical reentry site of VT2 was located at anatomical isthmus 4 (isthmus between VSD-patch and TA) and the VT demonstrated cw rotation through isthmus 4. PV, pulmonary valve; TA, tricuspid annulus; VSD, ventricular septal defect; VT, ventricular tachycardia.

two anatomical isthmuses bordered by EUS; isthmus 1 between a longitudinal EUS area (consistent with the previous anterior RV incision) and the TA and isthmus 3 bordered by an area of EUS in continuity with the TA consistent with the VSD patch and the PV. A good PM for the presumed clinical VT was obtained at isthmus 3. Activation mapping was consistent with counterclockwise propagation (late transition in precordial lead V₆) through isthmus 3. Entrainment mapping at this site revealed a central isthmus site and RF slowed and terminated the VT within 10 seconds, rendering the VT non-inducible. A linear RF lesion was performed to connect the areas of EUS. However, the activation sequence during pacing proximal to the line was still consistent with conduction through the isthmus.

After 3 months VT recurred. At repeat study the same VT was inducible. Although double potentials could be recorded along isthmus 3 during sinus rhythm, differential pacing was consistent with persistent slow conduction through the isthmus. During VT diastolic activity could be recorded within isthmus 3 and RF delivery resulted in delay and late termination of VT, but the VT remained inducible. Mapping at the left side of the region from within the right coronary cusp (RCC) revealed diastolic activity (30 msec before the earliest activation in the RVOT) and entrainment consistent with an isthmus site (figure 5). RF ablation at that site terminated VT within 5 seconds and prevented VT re-induction. Differential pacing

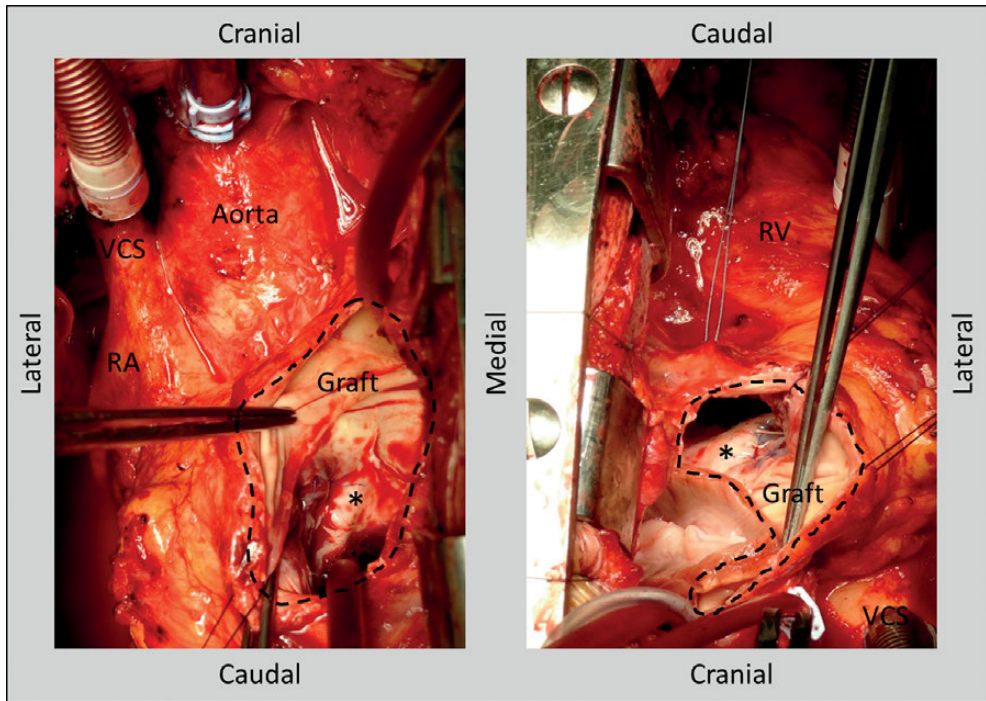


Figure 4. Intraoperative view of pulmonary valve replacement by pulmonary homograft in a patient with repaired Tetralogy of Fallot. Left panel a cranial (top) to caudal view, right panel a caudal to cranial view. The anterior suture line is marked with the dashed line in both pictures. At both panels the pulmonary homograft is held by the forceps. The pulmonary homograft is already posteriorly sutured to the VSD-patch (marked with *). After complete implantation of the homograft, important parts of the RVOT endocardium and in particular the infundibular septum are covered by the homograft. * = VSD-patch; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; TA = tricuspid annulus; VCS = vena cava superior; VSD = ventricle septum defect.

performed from the RVOT was consistent with conduction block. The patient continued with a low dose of Sotalol and remained free of VT during 15 months of follow-up.

Case 3

A 45 year old male with rTOF (operation reports not available) who had undergone CRT-D implantation for VTs and progressive heart failure was referred for VT ablation after prior ablation attempts in other centers had failed. Two VTs were inducible (VT1, cycle length 370ms and VT2, cycle length 380ms). RV EAM revealed a small low voltage area in the RV free wall perhaps consistent with a prior incision and a second low voltage area at the septum bordered by the TA and an area of EUS in continuity with the PV most likely consistent with a VSD patch. Hence, two anatomical isthmuses were identified: isthmus 1 between the TA and the small free wall scar and isthmus 4 between the VSD-patch and the TA. VT1 could

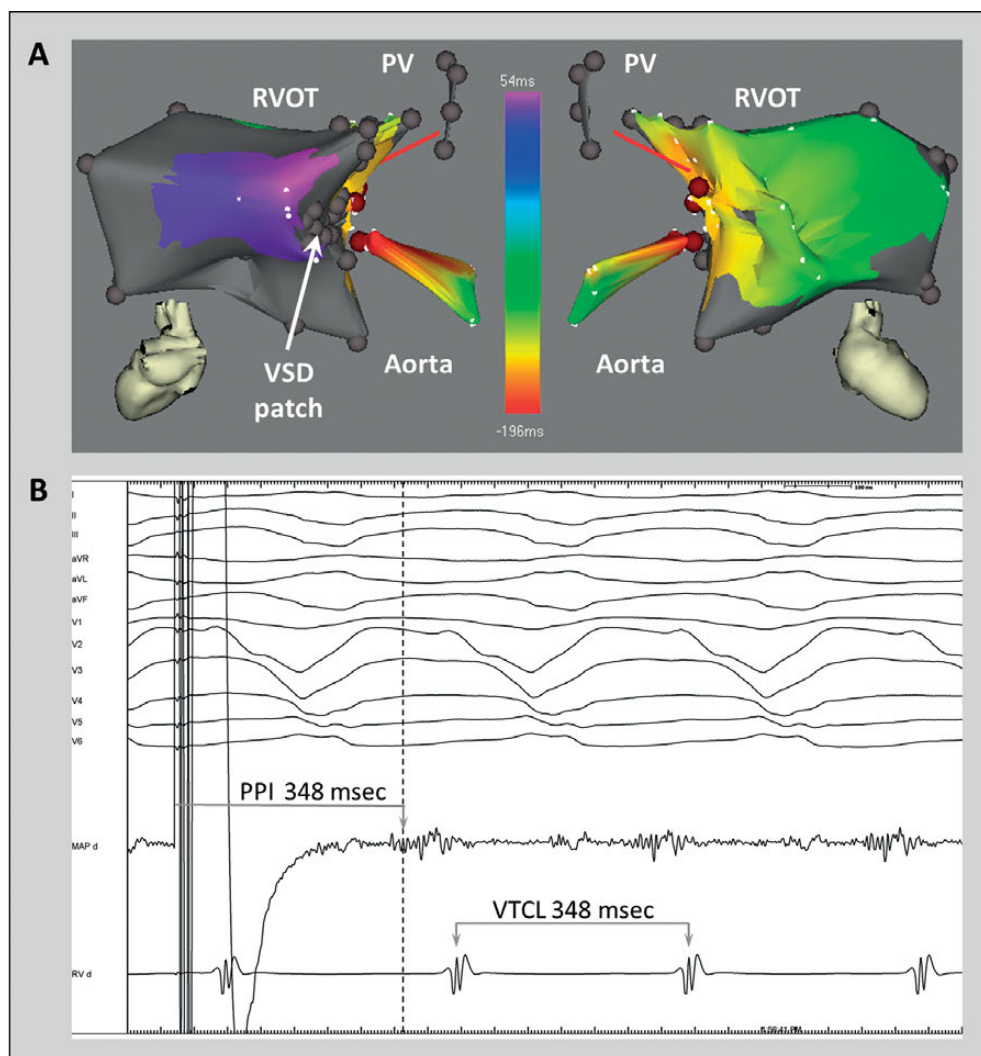


Figure 5. Panel A: Electroanatomical activation map of the clinical VT (activation time color coded according to bar) in left posterior and right lateral views. Earliest RVOT activation was recorded at the anatomical isthmus between the PV and VSD-patch. Diastolic activity preceding RVOT activation by 30 msec could be recorded from the aortic root. Panel B: From the aortic site VT could be entrained with concealed fusion ($PPI=VTCL=348$ ms). RF at this side terminated VT within 5 seconds. MAP d = bipolar recording of the distal mapping catheter; PPI = post pacing interval; PV = pulmonary valve; RVa = right ventricular apex; RVOT = right ventricular outflow tract; VSD = ventricular septal defect; VT = ventricular tachycardia; VTCL = VT cycle length.

be mapped to isthmus 1 and was ablated by connecting the presumed prior incision with the TA.

During VT2 (figure 3), presystolic activity was recorded at the lower edge of the presumed VSD patch with clockwise propagation through isthmus 4. However, the appearance of

the electrogram was consistent with a far-field signal and RF delivery did not terminate VT. At the adjacent LV site a good PM for VT2 was obtained, diastolic activity was present during VT, and a His-bundle electrogram was present in sinus rhythm. RF ablation was performed and resulted, as anticipated, in complete heart block. Thereafter, VT was no longer inducible. Sotalol was continued. He remained free of VT during 40 months of follow-up. He received one ICD shock for ventricular fibrillation after 15 months.

Case 4

A 36 year old male with rTOF (operation report not available) who had undergone ICD implantation and a previous VT-ablation in another center presented with an electrical storm and multiple ICD shocks. The presumed clinical VT (cycle length 345ms) was induced (figure 3). RV EAM identified isthmus 1 between EUS in the anterior RVOT in continuity with the PV and isthmus 3 bordered by EUS in continuity with the TA (VSD patch) and the PV. Entrainment at the ventriculo-infundibular fold was compatible with a VT entrance site and clockwise activation (QR in V1) of isthmus 3. However, RF at this site did not terminate VT. At the opposite side in the aorta, between the RCC and the NCC, a late potential (220 msec after QRS offset) was recorded during SR (figure 6). During VT mid diastolic activity was present and entrainment was consistent with an central isthmus site. A single RF application terminated VT within 10 seconds and prevented subsequent VT induction. To minimize procedural risks, no additional RF applications were performed in the aortic root.

VT recurred after 1 month and a repeat procedure was performed. The previous recorded VT could be induced. Activation mapping confirmed a reentry circuit entrance at the ventriculo-infundibular fold and an exit at the RCC region. A line of RF lesions was placed across isthmus 3 from the RV, the LVOT and the area between the LCC and RCC, abolishing inducible VT. The patient was discharged on nadolol and remained free of VT during 3 months of follow-up.

DISCUSSION

A right-sided RFCA approach for VT in rTOF targeting anatomical isthmuses failed to abolish inducible VT in 39% of our rTOF patients. Of importance, the majority (8/11) of these patients had a proven VT substrate involving anatomical isthmuses located at the infundibular septum. In all 4 patients in whom a left-sided approach was performed after right-sided ablation failure diastolic activity and/or concealed entrainment could be recorded either from the aortic root in muscular continuity and opposite to isthmus 3 (figure 7) or in the LVOT at the left sided inferior border of the VSD patch consistent with isthmus 4. RFCA at these sites terminated VT and/or prevented VT re-induction. The left-sided approach resulted in complete elimination of inducible VT and prevention of VT recurrence during follow-up (20±15 months) without procedure related complications in all cases, although one patient required two left-sided procedures. Based on the operation records, intraoperative and EAM findings the critical isthmus could likely not be transected from the right side due to

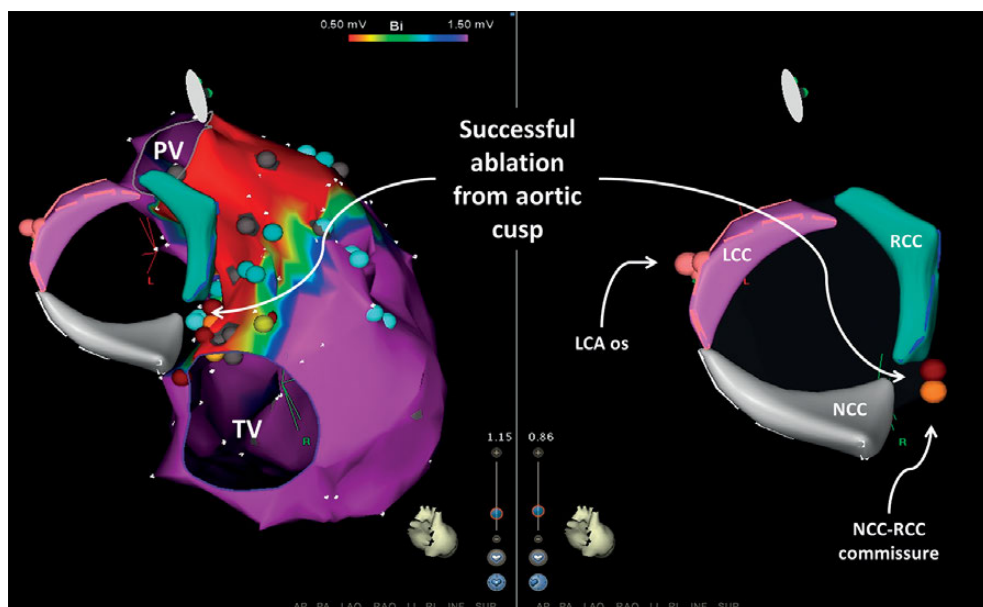


Figure 6. Electroanatomical voltage map (voltage color coded according to bar) of the right ventricle (RV) and coronary cusps in a modified right posterior view. After failed ablation in RV, the aortic root was mapped (cusp anatomy visualized by intracardiac echo using CartoSound® technology). During SR a late potential could be recorded between the NCC and RCC and during VT entrainment was consistent with an isthmus site. A single RF application terminated VT within 10 seconds. LCA = left coronary artery; L/N/RCC = left/non/right coronary cusp; PV= pulmonary valve; TV = tricuspid valve.

hypertrophic myocardium (case 2 and 4), overlying parts of a homograft (case 1) or overlying VSD patch material (case 3).

Anatomical considerations

The outlet septum as important feature of TOF and substrate for VA

TOF is characterized by a (sub)pulmonary stenosis, overriding aorta, VSD and RV hypertrophy.¹⁰ Probably the most important pathologic feature of TOF is anterior displacement of the infundibular septum which results in a subaortic VSD, subpulmonary stenosis and dextroposition of the aorta overriding the ventricular septum. The infundibular septum, i.e. outlet septum, is located between the ventriculo-infundibular fold and the trabeculo septomarginalis and cannot be recognized as a separate structure in the normal heart.^{10, 11} However in TOF, the infundibular septum can be recognized due to its anterior displacement located between the narrowed pulmonary outflow tract and the aortic valve (figure 7 and 8).^{10, 11} The outlet septum in TOF is therefore approachable from the right side (RV and RVOT) and left side (LV, LVOT and aortic root) (figure 7). The thickness of the infundibular septum in TOF can vary from thin fibrous tissue to severely hypertrophied myocardium.^{10, 11}

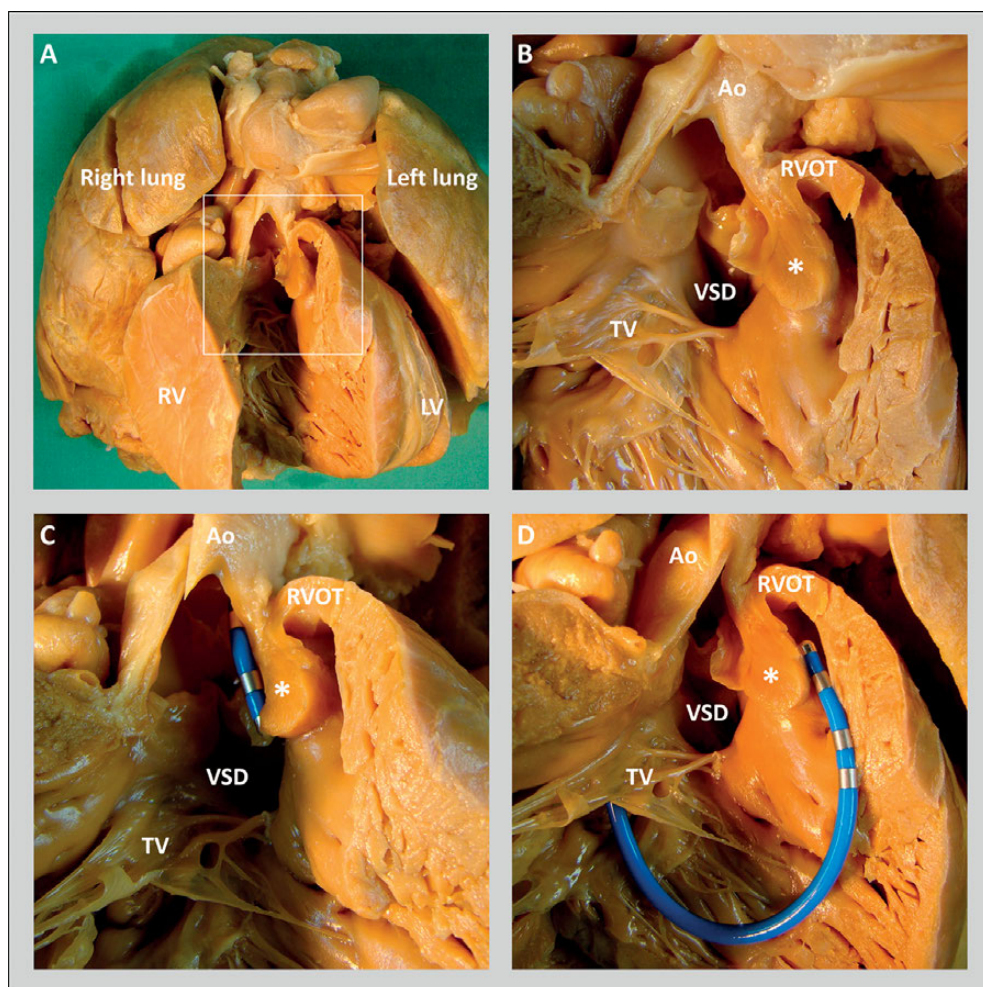


Figure 7. Right ventricular view of a post-mortem specimen with unrepaired Tetralogy of Fallot (4 years old). Panel A provides an overview. Panel B, C and D show the relation between the aorta and outlet septum (*) in detail. The catheter at panel C is positioned in the left coronary cusp. The catheter at panel D is positioned at the pulmonary side of the outlet septum. Please note the spatial relationship between the outlet septum and the sinus of the aorta. Ao = Aorta; LV = left ventricle; RVOT = pulmonary outflow tract; RV = right ventricle; TV = tricuspid valve; VSD = ventricular septal defect; * = outlet septum.

Histological study of the crista supraventricularis (i.e. outlet septum) in TOF have demonstrated that (ultra)structural abnormalities (interstitial fibrosis in 65% of the cases) are already present before surgical correction.¹² These (ultra)structural abnormalities and the surgical correction cause myocardial scarring that may provide the substrate for slow conduction and may explain the importance of the infundibular septum for reentry VT.

Prosthetic material and ablation failure

During the primary repair, the VSD is closed with a patch and the (sub)pulmonary stenosis is relieved by resection of the hypertrophied infundibulum and/or a (transannular) patch with additional commissurotomy in some cases.¹³ After correction, the infundibular septum (i.e. the deviated outlet septum) can remain a hypertrophied, muscular structure (figure 8) bordered by PV and VSD (patch). To transect this anatomical isthmus (isthmus 3) ablation from both the right and left side may be required (figure 7 and 8). Pulmonary valve regurgitation, in particular after placement of a transannular patch may require PVR after initial total correction.¹⁴ Mosaic porcine, bovine pericardial, or homograft prostheses are used. Parts of the prostheses may extend towards the VSD patch thereby covering important parts of the infundibular septum (see figure 4). Accordingly the anatomical isthmus between the PV and the VSD may no longer be approachable for catheter ablation from the RV endocardium, and may therefore require a left-sided approach as demonstrated in case 1. Although not observed in our series the combination of graft material and hypertrophy may prevent effective RFCA after PVR even if a combined approach is used. Therefore we feel that preoperative EP study and intraoperative ablation of anatomical isthmuses related to VT is a reasonable consideration even in the absence of spontaneous VTs.

Potential complications

In patients with a muscular VSD, which is present in approximately 20% of TOF patients, the posteroinferior border of the VSD is a muscular rim, which is often only a few millimeters broad. This anatomical isthmus (isthmus 4) is thus bordered by the VSD (patch) and the TA. Importantly, isthmus 4 can be partly covered by the VSD-patch, which is usually stitched some millimeters away from the edge of the rim to avoid damage to the His-bundle.¹³ Therefore a left-sided approach may be required to transect parts of the isthmus covered by the patch. However, due to the proximity of the His-bundle there is a risk of total AV block with the consequent need for (bi)ventricular pacing, as illustrated in case 3.

In this small series no other complications were observed. However, ablation in the aortic sinuses has a risk of coronary injury and the location of the coronary ostia should be visualized by angiography considering the potential for anatomical variation in TOF. RF ablation in the aortic root could also theoretically damage the aortic valve.

CONCLUSION

Although VT in Tetralogy of Fallot is primarily right ventricular in origin, ablation from the left ventricle or aorta is required to interrupt some anatomical isthmuses bordering on the infundibular septum. Our limited series suggests that this approach may be of benefit to a significant number of patients in whom a right-sided approach fails. The proximity of the coronary arteries and the cardiac conduction system needs to be considered.

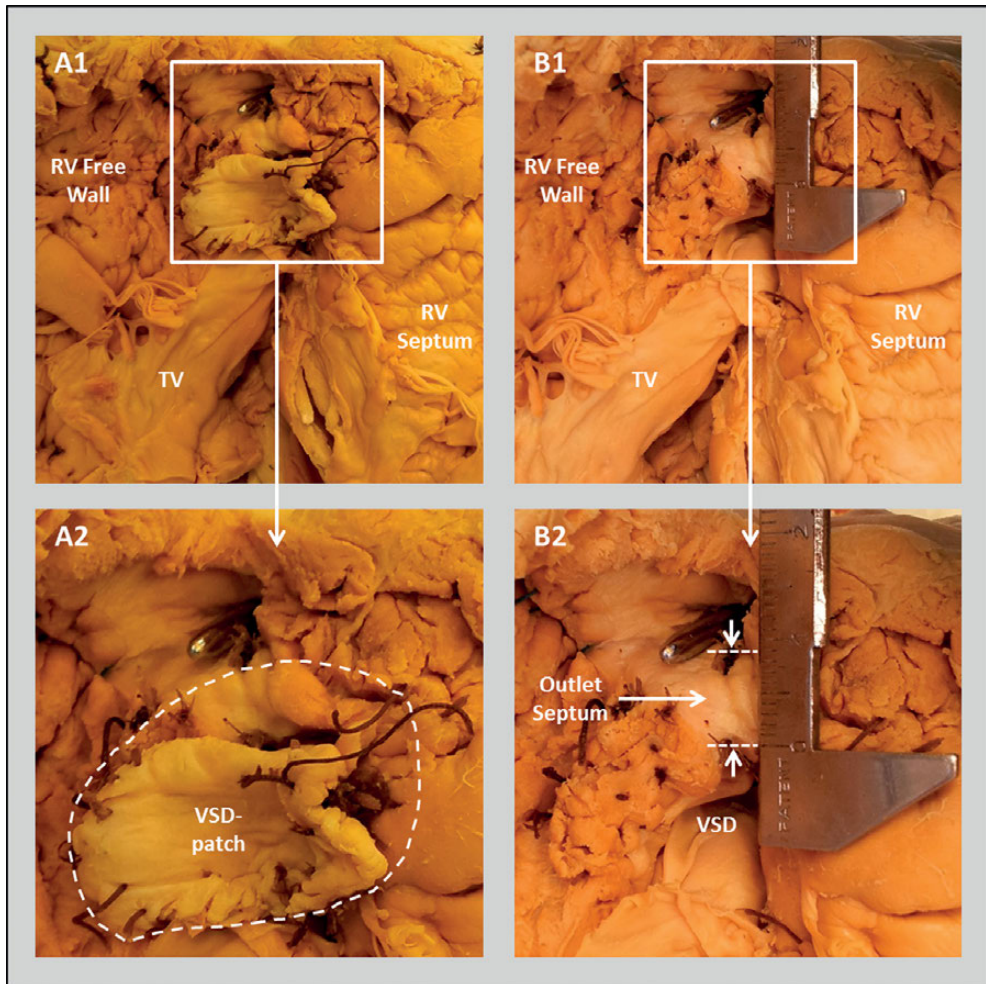


Figure 8. Right ventricular view of a post-mortem specimen with repaired Tetralogy of Fallot (24 years old). The correction consisted of infundibular resection and patch closure of a perimembranous VSD. Panel A1 and B1 provide an overview, panel A2 and B2 show the infundibulum and VSD in detail. The prior location of the VSD-patch (partly removed) is illustrated with the dashed circle in panel A2, the VSD-patch is removed in panel B1-2. A probe was inserted in the pulmonary artery (*not visible*) and advanced through the pulmonary valve (*not visible*) into the infundibulum (*visible*). The probe is located on the pulmonary side of the outlet septum, i.e. the isthmus between the VSD and pulmonary valve. B2, the outlet septum is marked by two dashed lines and perpendicular directed arrows, please note the thickness of the septum (9 mm) even after the correction. RV = right ventricular; TV = Tricuspid Valve; VSD = ventricular septal defect.

ACKNOWLEDGMENTS

We wish to thank R. Slagter for the design of figure 1. We wish to thank M. Bartelings for the photos of picture 8.

CLINICAL PERSPECTIVE

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Ventricular arrhythmias are an important cause for late morbidity and mortality in a growing population of adults with repaired Tetralogy of Fallot. The majority of these ventricular arrhythmias are re-entrant ventricular tachycardias (VTs), which are related to anatomic isthmuses usually approached from the right ventricle. These VTs can be successfully treated with radiofrequency catheter ablation (RFCA) provided that the anatomic isthmus can be completely transected. In the present study performed in 28 consecutive repaired Tetralogy of Fallot patients, right-sided RFCA failed to abolish the VTs in 11 (39%) patients. Of importance, in 8 of 11 patients, the VT was mapped to a septal anatomic isthmus. In 4 of 8 patients, an additional left-sided approach was performed, and in all 4, the anatomic isthmus could be successfully transected from the left, resulting in noninducibility and freedom of VT recurrence during follow-up. RFCA was performed from the aortic root in 3 patients and in 1 patient, with a biventricular implantable cardioverter-defibrillator, from the left side of the septum in proximity to the His-bundle, followed by anticipated atrioventricular block. Based on the demonstrated anatomic and intraoperative observations, right-sided RFCA failure was likely because of the septal hypertrophied myocardium, the overlying pulmonary homograft, and overlying ventricular septal defect patch. A left-sided ablation approach should be considered in repaired Tetralogy of Fallot patients in whom right-sided RFCA of a septal anatomic isthmus failed. Knowledge of the anatomy, the type of repair, and reoperations are helpful to plan the procedure and to anticipate potential complications.

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Slow Conducting Electroanatomical Isthmuses: An Important Link between QRS Duration and VT in Tetralogy of Fallot

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ABSTRACT

Background

QRS prolongation has been associated with ventricular tachycardia (VT) in repaired Tetralogy of Fallot (rTOF).

Objectives

To evaluate the influence of slow conducting anatomical isthmuses (SCAI) as dominant VT substrate on QRS duration.

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Methods

Seventy-eight rTOF patients (37 ± 15 years, 52 male, QRS 153 ± 29 ms, 67 RBBB) underwent programmed stimulation and electroanatomical activation mapping during sinus rhythm. RV surface, RV activation pattern, RV activation time (RVAT), conduction velocity (CV) at anatomical isthmuses (AI) and remote RV sites were determined.

Results

Twenty-four patients were inducible for VT (VT+); SCAI was present in 22/24 VT+ but only in 2/54 patients without inducible VT (VT-). CV through AI was slower in VT+ (0.3 (0.3 - 0.4) vs. 0.7 (0.6 - 0.9)m/s, $p < 0.01$) but CV in the remote RV did not differ between groups. In non-RBBB, QRS duration was similar in VT+ ($n=6$) and VT- ($n=5$), but RV activation within SCAI exceeded QRS-offset in VT+ (37 ± 20 vs. -5 ± 9 ms, $p < 0.01$). In RBBB, both QRS duration and RVAT were longer in VT+ ($n=18$, 17/18 QRS > 150 ms) compared to VT- ($n=49$, 27/49 QRS > 150 ms) (173 ± 22 vs. 156 ± 20 ms, $p < 0.01$; 141 ± 22 vs. 129 ± 21 ms, $p = 0.04$). In VT+ patients, QRS prolongation > 150 ms ($n=17$) was due to SCAI or blocked isthmus in 15 (88%) and 1 (6%). In contrast, in VT- patients, QRS prolongation > 150 ms ($n=27$) was due to enlarged RV or blocked isthmus in 10 (37%) and 8 (30%), but due to SCAI in only 1 (4%). After exclusion of a severely enlarged RV, a QRS duration > 150 ms was highly predictive for SCAI/blocked AI (OR 16.6 (95%CI, 3.3– 84, $p < 0.01$).

Conclusions

A narrow QRS does not exclude VT-related SCAI. In the presence of a RBBB, SCAI further prolongs QRS duration. A QRS > 150 ms is highly suspicious for a SCAI or isthmus block distinguishable by electroanatomical mapping.

INTRODUCTION

As a result of earlier repair and evolving surgical techniques, the majority of patients with repaired Tetralogy of Fallot (rTOF) survive to adulthood,¹⁻³ but may remain at risk of sudden cardiac death (SCD) due to ventricular arrhythmias (VA).^{4, 5} Monomorphic ventricular tachycardia (VT) is the most common arrhythmia subtype affecting >14% of patients and account for >80% of appropriate ICD therapies.^{6, 7} Over the last decades, efforts have been made to non-invasively identify rTOF patients at risk for VT. Although no single risk factor has shown sufficient independent predictive value for the presence of an arrhythmic substrate in an individual patient, a prolonged QRS duration >180ms has consistently been associated with VT and SCD.⁸⁻¹⁰ In contemporary cohorts, a lower QRS cut-off value to identify a patient at risk has been suggested and attributed to advances in surgical approaches.^{11, 12} The modern transatrial-transpulmonary surgical approach with smaller transannular patches may not only prevent severe pulmonary valve regurgitation and right ventricular (RV) dilatation but also right bundle branch damage. Accordingly, contemporary rTOF patients may have less RV dilatation, different RV activation patterns and even a narrow postoperative QRS.¹³ QRS prolongation was initially thought to be the combined effect of a surgical created right bundle branch block (RBBB) and progressive, RV dilatation with global conduction delay, the latter creating a substrate for VT.⁹ However, invasive electroanatomical mapping studies have demonstrated that the dominant substrate for VT are slow conducting anatomical isthmuses (SCAI) confined to the RV outflow tract (RVOT).¹⁴ We hypothesize that the interplay between a postoperative RBBB and conduction delay in SCAI determines the RV activation pattern and QRS prolongation. The objective of this study is to evaluate, with the use of invasive electroanatomical mapping, if QRS prolongation is due to localized conduction delay across SCAI, rather than due to global conduction delay.

METHODS

Patient selection

The cohort consisted of 83 consecutive rTOF patients with either documented sustained VT, or considered at risk for VT and/or with indication for re-operation who underwent electrophysiological evaluation and RV electroanatomical mapping (EAM) between 2005 and 2013 at Leiden University Medical Center (n=53) and Bordeaux University Hospital (n=30). Patients were considered at risk for VT if ≥ 1 of the following risk factors was present: syncope, non-sustained VT on Holter, QRS duration ≥ 180 ms, late repair (≥ 5 years), at least moderately depressed RV or LV function or presence of a transannular-patch.^{9, 10, 15-19} The Dutch Central Committee on Human-related Research (CCMO) permits use of anonymous data without prior approval of an Institutional Review Board, if the data are obtained for patient care and if the data do not contain identifiers that could be traced back to the individual patient. All patients were treated according to our standard clinical protocol and provided informed consent.¹⁴

Baseline evaluation

Patient records were reviewed for date and type of repair, device implantation, and documented VA. Non-paced 12-lead ECGs recorded at 25mm/sec were assessed for QRS duration and intraventricular conduction disturbances. In 53/83 patients, QRS duration was also measured using LEADS (supplemental methods 1).²⁰ Holter recordings were reviewed for non-sustained VT. Right and left ventricular (LV) cardiac function was assessed by cardiac magnetic resonance imaging (CMR) and/or echocardiography. A mildly reduced or good RV function (RV ejection fraction >40%) with a tricuspid plane systolic excursion ≥ 14 mm and a LV ejection fraction $\geq 40\%$ were classified as preserved RV and LV function, respectively.²¹ Cardiac volumes were determined by CMR and indexed for body surface area. RV end diastolic volume index (RVEDVi) ≥ 180 ml/m² was considered severely enlarged.²²

Electroanatomical mapping and electrophysiological evaluation

Programmed electrical stimulation (PES) was performed (supplemental methods 2). Sustained VT was defined as lasting ≥ 30 seconds or causing hemodynamic compromise requiring termination. A detailed 3D EAM of the RV was constructed during sinus rhythm (SR) using a non-fluoroscopic mapping system (Carto3 & CartoXP, Biosense Webster). The endocardial RV surface was measured using dedicated tools of the CARTO system. EAM RV surface was compared to CMR-derived volume. All mapping points were reviewed offline for correct annotation of the local activation time (LAT), defined as the sharp bipolar electrogram coinciding with the fast down-stroke of the unipolar electrogram. All activation maps were displayed as isochronal maps and as propagation maps (online videos) to determine RV activation pattern. The site(s) of earliest and latest RV activation were identified and the total RV activation time was calculated. Earliest onset and latest offset of the QRS-complex in any lead were annotated on CARTO to assess QRS duration. QRS duration, total RV activation time (RVAT), and intervals between onset of QRS and onset of RV activation, and between offset of QRS and offset of RV activation were measured using electronic calipers (sweep speed 200mm/s, figure 1).

Anatomical isthmus characteristics and its relation to ventricular tachycardia

The identification of anatomical isthmuses (AIs) in rTOF has been described in detail (supplemental methods 3).²³ Isthmus 1 is located between the tricuspid annulus (TA) and the RVOT-patch/RV-incision; isthmus 2 between the RV-incision and the pulmonary valve (PV). Isthmus 3 and 4 are located at the infundibular septum, with isthmus 3 between PV and VSD-patch, and isthmus 4 between VSD-patch and TA.²³ The electroanatomical characteristics of each identified AI were assessed. The fill threshold for EAM of the AI was set at ≤ 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 sites.¹⁴ Isthmus length is the distance between entrance and exit sites and the conduction time through the isthmus

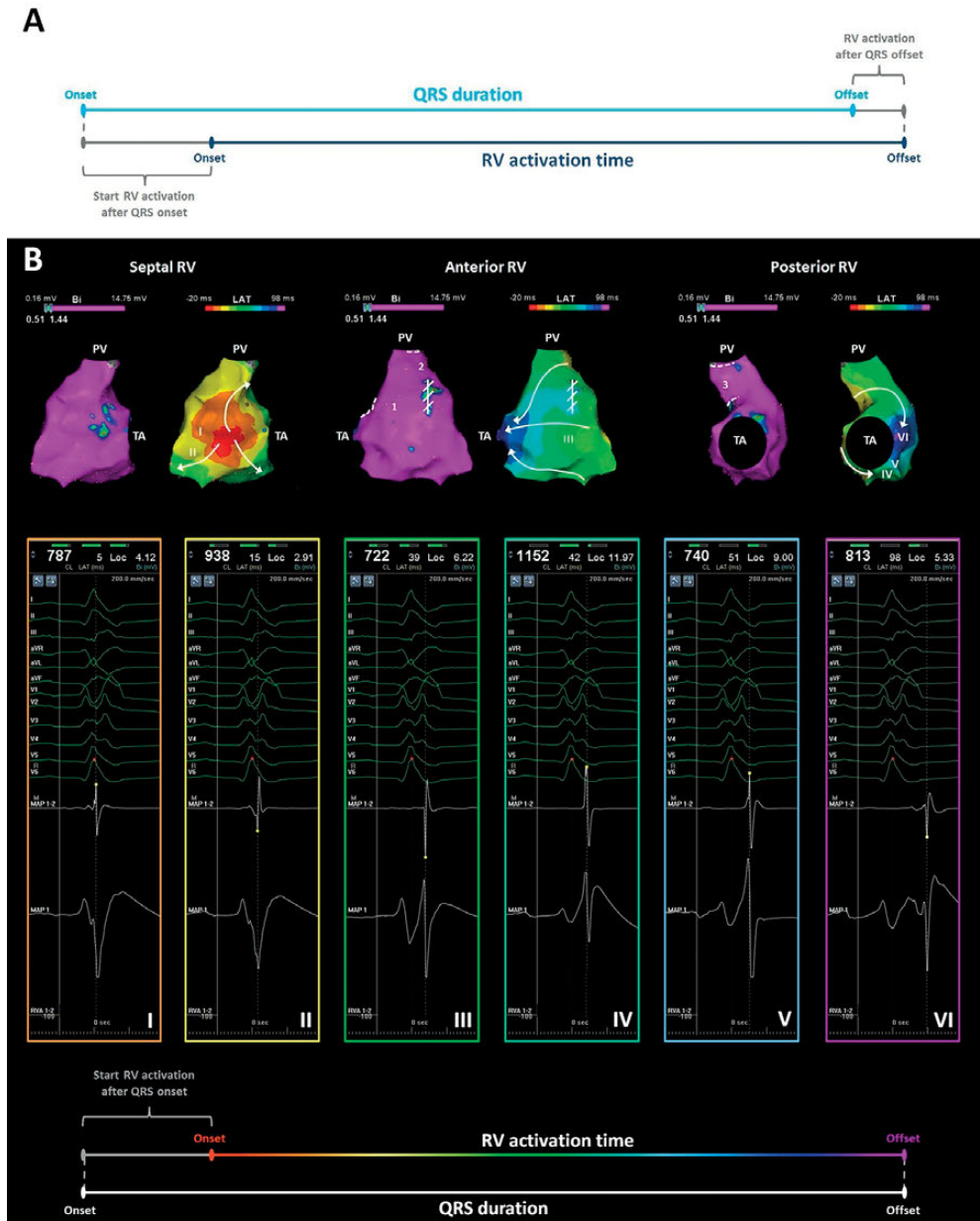


Figure 1. Activation time measurements. Panel A: Schematic of QRS and RV activation time measurements. Panel B: RV electroanatomical map (EAM) of a patient (RBBB, QRS 132ms) in three views displayed as bipolar voltage map (left) and activation map (right). Voltage and local activation time (LAT) are color coded. Three anatomical isthmuses are shown: isthmus 1 (between tricuspid annulus (TA) and RV-incision), isthmus 2 (between RV-incision and pulmonary valve (PV)) and isthmus 3 (between PV and VSD-patch). Total RV activation time is 108ms with earliest RV activation at the septum after QRS-onset and latest activation at the lateral TA coinciding with QRS-offset as demonstrated in the lower schematic.

is the difference between the LAT at isthmus entrance and exit. The isthmus conduction velocity (CV) was calculated (isthmus length/conduction time). The CV was measured in the direction of the RV propagation wave front during sinus rhythm. In selected patients, we have performed differential pacing close to the anatomical isthmus to differentiate between slow conduction and block. A slow conducting AI (SCAI) was defined as isthmus with low bipolar voltage electrograms ($<1.5\text{mV}$) and a $\text{CV} < 0.50\text{m/sec}$.¹⁴ Based on the first quartile of CV distribution in normal controls, a $\text{CV} \geq 0.50\text{m/s}$ and $\leq 0.63\text{m/s}$ was considered borderline CV.¹⁴ An AI was classified as having a pre-existing conduction block if either no excitable tissue between its anatomical boundaries could be identified or double potentials could be recorded along the AI and in addition the RV activation sequence during SR was consistent with propagation towards the isthmus from both sites. Septal block was defined as a pre-existing conduction block at isthmus 3 in case of perimembranous VSD (absence of isthmus 4) or as a pre-existing conduction block at both isthmus 3 and 4 in case of muscular VSD. Whether an induced VT was dependent on a SCAI was determined by pace-mapping ($\geq 11/12$ pace-match) and/or concealed entrainment and/or diastolic activation during VT with VT termination by RF-delivery.²³ To compare CV within and remote from AI the CV was calculated for three additional RV areas: RV septum, RV free wall and low RVOT free wall (supplemental methods 4).

Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation (SD) or median with inter quartile range (IQR) according to distribution. Categorical data are reported as percentages or frequencies. The difference in QRS duration measured with LEADs on 12-lead ECG and using Carto system was assessed by paired student's T-test. Patients with and without VT were compared using a Student-T, Mann-Whitney U and Chi-Square test where appropriate, including subgroups. Associations between QRS duration, RV volumes on CMR and RV area on EAM were assessed by Pearson correlation. The relation between (i) QRS duration and total RV activation time and (ii) QRS duration and RV activation after QRS-offset was illustrated with a scatterplot for all patients and patients with(out) RBBB, dots were marked for VT inducibility. QRS duration of RBBB patients were illustrated with an aligned scatterplot, according to VT profile. In addition, in these patients, the odds ratio of QRS duration of $>150\text{ms}$ was calculated for AI properties using logistic regression. SPSS 22.0 for Windows was used. $P < 0.05$ was considered significant.

RESULTS

Patient Population

Eighty-three patients underwent electrophysiological evaluation. Five patients with an incomplete RV map or maps acquired during ventricular pacing were excluded. One patient had undergone a prior VT ablation in another center. Subsequently, the study population consisted of 78 patients (37 ± 15 years, 67% male) who were repaired at a median age of 5.0

years (2.1-8.5). Eleven (14%) had documented sustained VT. QRS duration was 153 ± 29 ms. Sixty-seven patients (86%) had a broad QRS (>120 ms), all RBBB configuration, and 11 patients had a narrow QRS. Thirteen patients (17%) had QRS duration ≥ 180 ms. All but 2 patients had a preserved LV function and 47 (60%) a preserved RV function. Baseline characteristics are provided in table 1.

Electroanatomical mapping and electrophysiological evaluation

RV activation time during SR was 130 ± 24 ms. QRS duration did not differ when measured on pre-procedural 12-lead ECGs or on CARTO (-1.8 ms (95%CI, -4.0 – 0.4 ms) $p=0.11$). The electroanatomical RV surface was 249 ± 66 cm² and showed a significant correlation with the RVEDV derived from CMR ($r=0.68$, $p<0.001$, online figure 1). A RVEDVi of >180 ml/m² (severely dilated RV) corresponded to a RV surface of >293 cm² observed in 15 patients (19%). For the entire population, neither the RV surface nor the RV volume correlated to QRS duration ($r=0.14$, $p=0.22$; $r=0.07$, $p=0.55$, respectively, online figure 2).

Table 1. Baseline characteristics

	All patients (n=78)
Age (years)	37 $\pm$ 15
Gender (male)	52 (67%)
Total Repair Age (years)	5.0 (2.1-8.5)
Total Repair Age ≥ 5 years	40 (51%)
TA-patch	29/67* (43%)
Time after repair (years)	30 $\pm$ 11
PVR (yes)	16 (21%)
PVR age (years)	31 $\pm$ 13
Syncope	5 (6%)
QRS duration	153 $\pm$ 29
QRS duration ≥ 180 msec	13 (17%)
Right bundle branch block	67 (86%)
Non-sustained VT on Holter	16/66* (24%)
Class III antiarrhythmic drugs	2 (3%)
LV function preserved	76 (97%)
RV function preserved	47 (60%)
RVEDV (ml)	242 $\pm$ 73
RVEDV index (ml/m ²)	136 $\pm$ 39
RVEDV ≥ 180 ml/m ²	8/68 (12%)
RVESV (ml)	138 $\pm$ 54
RVESV indexed (ml/m ²)	78 $\pm$ 30
Cardiac function preserved	46 (59%)

RVEDV, RV end-diastolic-volume; RVESV, RV end-systolic-volume; LAFB, left anterior fascicular block; LV, left ventricular; Pts, patients; PVR, pulmonary valve replacement; RBBB, right bundle branch block; RV, right ventricular; TA-patch, transannular patch; *, reports available.

Anatomical isthmus characteristics and its relation to ventricular tachycardia

All patients had at least one AI and 24 (31%) at least one SCAI, which was SCAI 3 in the majority (21/24). One of the 21 patients with SCAI 3 had normal conduction through isthmus 4, compensating for septal conduction delay, and one patient had only septal SCAI 4. Accordingly, 21 out of 24 patients with any SCAI showed slow conduction at the infundibular septum. In 9 patients, a pre-existing block of an AI was observed which was septal isthmus 3 in all. Thirteen patients had at least one AI with borderline CV, which was also isthmus 3 in all.

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Twenty-four (31%) patients (including all 11 patients with spontaneous VT) were inducible for a total of 34 VTs (median VTCL 247ms [230–287]). In 22 patients (92%) with 32 VTs, a SCAI was the substrate for all clinical and induced VTs (supplemental results 1), which was a septal SCAI (3 or 4) in 19 of 22 patients (86%). There was no difference in AI CV between the 11 patients with spontaneous and inducible VT (median 0.27m/s (0.20–0.32)) and the 13 patients with only inducible VT (median 0.34m/s (0.29–0.42), $p=0.16$). In contrast, a SCAI was found in only 2 of 54 patients (4%) without documented or induced VT. Slow conduction was not observed remote from the AIs. The electroanatomical CVs for the RV septum, RV free wall and RVOT free wall were 1.3 ± 0.3 m/s, 1.3 ± 0.3 m/s and 0.9 ± 0.2 m/s respectively and did not differ between patients with or without VT. Fourteen of the 22 patients with SCAI related VT underwent successful ablation, defined as non-inducibility of any VT and transection of the SCAI. Two patients had no VT, but did have a SCAI 3 and underwent successful ablation defined as bidirectional block of the SCAI. All 68 patients without a SCAI (52 at baseline, 16 after ablation) remained free from VT during follow-up (39 ± 24 months). Detailed acute and long-term ablation outcome are added to the supplemental results 2.

QRS duration, RV activation time and pattern according to VT inducibility

For the entire population, QRS duration did not differ significantly between patients with and without VT (157 ± 35 ms versus 151 ± 25 ms, $p=0.411$). However, the RVAT was significantly longer in patients with VT (142 ± 23 ms versus 125 ± 23 ms in non-VT patients, $p=0.005$), table 2.

A subgroup analysis was performed according to presence or absence of RBBB:

1. In patients with *narrow QRS (non-RBBB)*, QRS duration was similar in patients with and without VT (108 ± 11 ms and 101 ± 11 ms, $p=0.429$) whereas the RVAT was longer in patients with VT (143 ± 30 ms vs 91 ± 12 ms in patients without VT, $p=0.017$). In all patients, the earliest RV activation during SR was observed simultaneously at the distal septum *and* at the anterior RV free wall followed by rapid propagation of activation wavefronts towards the lateral and septal RVOT. The onset of RV activation coincided or was close to the QRS-onset (3 ± 12) in patients with and without VT ($p=0.931$). However, QRS-offset and RV activation offset coincided only in those without VT. In non-RBBB patients with VT, the latest RV activation exceeded QRS-offset by 37 ± 20 ms (figure 2D-E and online figure 3) and was located at the exit

Table 2. QRS duration and RV activation times according to presence of VT and RBBB

	VT-	VT+	p
All patients	n = 54	n = 24	
QRS duration (ms)	151±25	157±35	0.411
RV activation time (ms)	125±23	142±23	0.005
Interval: QRS onset - RV onset (ms)	23±13	21±17	0.713
Interval: QRS offset - RV offset (ms)	-3±8	6±21	0.040
Non-RBBB	n = 5	n = 6	
QRS duration (ms)	101±11	108±11	0.429
RV activation time (ms)	91±12	143±30	0.017
Interval: QRS onset - RV onset (ms)	4±12	2±14	0.931
Interval: QRS offset - RV offset (ms)	-5±9	37±20	0.009
RBBB	n = 49	n = 18	
QRS duration (ms)	156±20	173±22	0.004
RV activation time (ms)	129±21	141±22	0.036
Interval: QRS onset - RV onset (ms)	25±12	28±13	0.305
Interval: QRS offset - RV offset (ms)	-3±9	-4±4	0.524

RBBB, right bundle branch block; RV, right ventricular; VT, ventricular tachycardia; VT -, not inducible for VT; VT+, inducible for VT.

site of the VT related SCAI in all patients. These small late activated areas with low bipolar voltages did not contribute to the 12-lead surface ECG as demonstrated in figure 3. RV size and RV CV remote from the AIs was similar between non-RBBB patients with and without VT, table 3.

2. In patients with a *RBBB*, both QRS duration and RVAT were longer in patients with VT as compared to patients without VT (173±22 and 141±22 versus 156±20 and 129±21, $p=0.004$ and $p=0.036$, respectively). Of interest, only 6/18 with VT had a QRS duration ≥ 180 ms, but all but one had a QRS duration >150 ms. In contrast, only 27 (55%) of the 49 RBBB patients without VT had QRS duration >150 ms. In all RBBB patients, earliest RV activation was observed in a broad area at the mid-to basal RV septum, but not at the RV free wall. In patients without VT and normal conducting AIs, activation propagated in different wave-fronts: from the RV septum through the septal AIs and AI 1, across the inferior wall *and* across the RV free wall, with fusion of wave fronts typically at the basal *lateral tricuspid annulus* being the latest RV activated area (figure 4, online video 1). In patients with VT and septal activation delay or delay in AI 1, the latest activated RV area shifted towards the lateral RVOT (figure 4, online video 2). The prolongation of the pathway for total RV activation resulted in both increase in RVAT and QRS duration. Of note, the same activation pattern and prolongation of RV activation and QRS duration was observed in 8 patients without VT and a preexisting septal isthmus block (excluding the septal isthmus as substrate for VT). In RBBB patients, the onset of

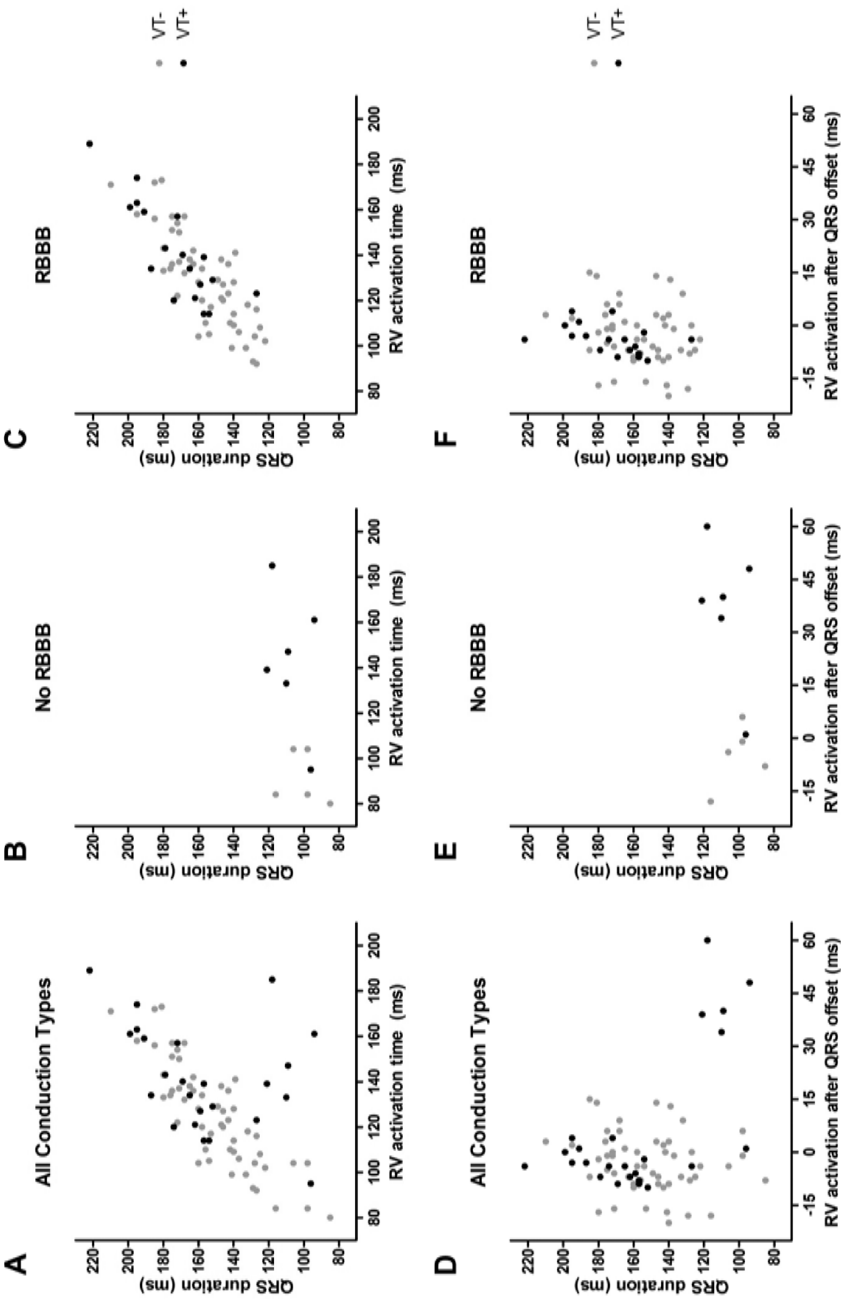


Figure 2. Relation between QRS duration and RV activation time. Scatterplots A-C: Relation between QRS duration and RV activation time for all patients (A), patients without RBBB (B), and with RBBB (C) according to VT inducibility (gray dots not inducible (VT-), black dots inducible for VT (VT+)). Scatterplots D-F: Relation between QRS duration and RV activation time after QRS-offset for all patients(D), patients without RBBB (E), and with RBBB (F). VT, ventricular tachycardia; RBBB, right bundle branch block.

Table 3. Right ventricular size, conduction velocity and anatomical isthmuses according to presence of VT and RBBB.

	VT-	VT+	p
Non-RBBB	n=5	n=6	
RV size (cm ²)	237±48	247±63	0.785
CV remote of AI			
RVOT free wall (m/s)	1.1±0.5	1.0±0.2	0.455
RV free wall (m/s)	1.4±0.4	1.4±0.2	0.800
RV septal (m/s)	1.3±0.4	1.3±0.1	0.929
Overall (m/s)	1.3±0.3	1.2±0.1	0.568
Anatomical isthmus			
SCAI present (yes)	0 (0%)	6 (100%)	0.001
SCAI (n)	0 (0-0)	2 (1-3)	0.004
SCAI, isthmus 1 (yes)	0 (0%)	3 (50%)	0.064
SCAI, isthmus 2 (yes)	0 (0%)	3 (50%)	0.064
SCAI, isthmus 3 (yes)	0 (0%)	5 (83%)	0.006
SCAI, isthmus 4 (yes)	0 (0%)	0 (0%)	
Longest AI conduction time (ms)	17±11	73±17	<0.001
Slowest AI CV (m/s)	0.8 (0.7-0.9)	0.3 (0.2-0.4)	0.004
Blocked septal anatomical isthmus	0 (0%)	0 (0%)	
RBBB	n=49	n=18	
RV size (cm ²)	254±64	241±79	0.489
CV remote of AI			
RVOT free wall (m/s)	0.9±0.2	0.9±0.3	0.997
RV free wall (m/s)	1.3±0.3	1.3±0.2	0.639
RV septal (m/s)	1.3±0.3	1.2±0.3	0.228
Overall (m/s)	1.2±0.2	1.1±0.1	0.307
Anatomical isthmus			
SCAI present (yes)	2 (4%)	16 (89%)	<0.001
SCAI (n)	0 (0-0)	1 (1-1)	<0.001
SCAI, isthmus 1 (yes)	0 (0%)	3 (17%)	0.003
SCAI, isthmus 2 (yes)	0 (0%)	1 (6%)	0.096
SCAI, isthmus 3 (yes)	2 (4%)	14 (78%)	<0.001
SCAI, isthmus 4 (yes)	0 (0%)	2 (11%)	0.018
Longest AI conduction time (ms)	22±12	65±29	<0.001
Slowest AI CV (m/s)	0.7 (0.6-0.9)	0.3 (0.2-0.4)	<0.001
Blocked septal anatomical isthmus	8 (16%)	1 (6%)	0.252

CV, conduction velocity; RBBB, right bundle branch block; RV, right ventricular; RVOT, RV outflow tract; SCAI, slow conducting anatomical isthmus; TA, tricuspid valve annulus; VT, ventricular tachycardia; VT -, not inducible for VT; VT+, inducible for VT.

the RV activation was recorded 26±12ms after the onset of the QRS both in patients with and without VT (p=0.305). Furthermore, QRS-offset and RV activation offset coincided (-3±8ms, p=0.524) in patients with and without VT (figure 2F and online

figure 3). As in patients with narrow QRS, CV of the RV remote from AIs and the RV endocardial surface did not differ between patients with and without VT (table 3).

Interplay between QRS-duration, RV size, SCAI and VT in patients with RBBB

Of the 18 patients with RBBB and VT, 17 had a QRS duration >150ms, 16 a SCAI, but only 4 a severely dilated RV (figure 5). Accordingly, in patients with RBBB and VT, a SCAI was the most prevalent mechanism for QRS prolongation. The only patient with a RBBB, VT and a QRS duration <150ms had a SCAI 3 related VT. However, the second fast conducting septal isthmus 4 prevented septal activation delay and QRS prolongation.

In contrast, of the 49 RBBB patients without VT, only 27 had a QRS duration >150ms. Of these 27 patients, the majority (n=16 (59%)) had either a severely enlarged RV without SCAI (n=10 (37%)) and/or a preexisting blocked septal isthmus (n=8 (30%)) as mechanisms for QRS prolongation (figure 5). In contrast, none of the 22 patients without VT and QRS

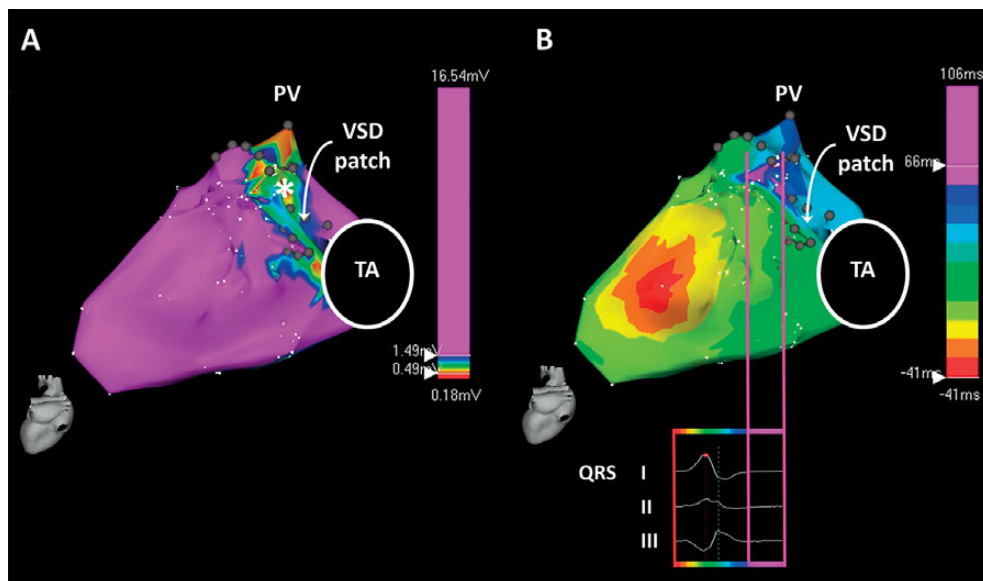


Figure 3. Patient without RBBB, but with VT. RV electroanatomical maps obtained during sinus rhythm of a 35 years old female, who presented with near-collapse, inducible for a fast VT (VTCL 230ms), modified posterior view. Left panel (A): Voltage map color-coded for bipolar voltage. Right panel (B): Activation map color-coded for activation time according to bar. QRS duration was 109ms (on/offset -43/66ms), the total RV activation time was 147ms (on/offset -41/106ms). RV activation exceeds QRS-offset (purple area on right map, not visible on ECG) by 40ms, the latest activated area was located in the low voltage area between the pulmonary valve (PV) and the VSD-patch (i.e. isthmus 3). There was capture at each site across isthmus 3 and fusion at the exit region of isthmus 3 suggesting slow conduction through isthmus 3. In addition, a slow conducting or blocked isthmus can be further differentiated by differential pacing close to the isthmus. At this site (*) of isthmus 3 the critical isthmus of the induced VT was identified. TA, tricuspid annulus.

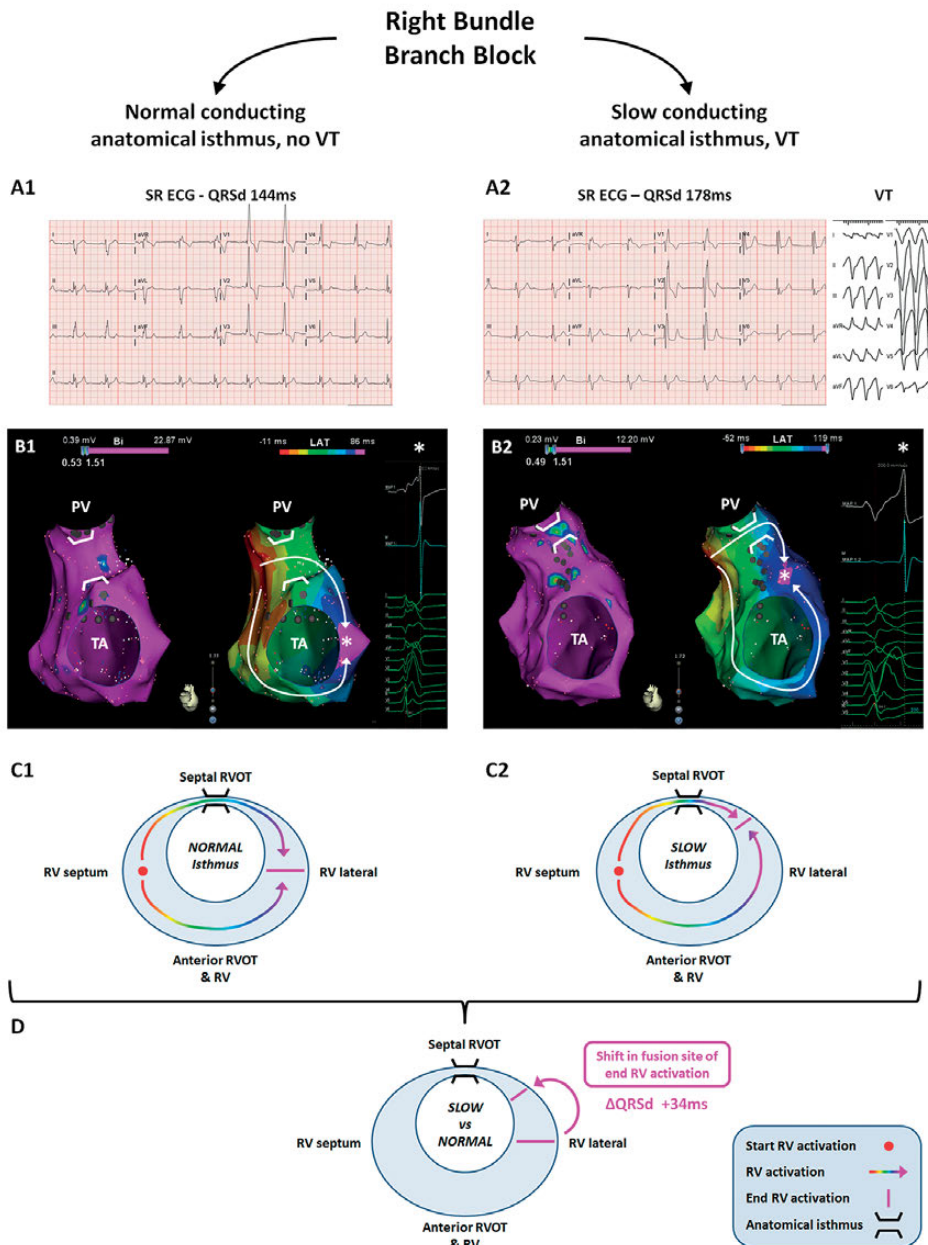


Figure 4. RV activation in patients with RBBB according to absence/presence of a slow conducting anatomical isthmus. Panel A1-2: 12-lead ECGs of a patient without VT (A1) and with VT (A2). Panel B1-2: Electroanatomical reconstruction of the RV (modified posterior view) displayed as color-coded voltage map (left, purple indicates normal bipolar voltage) and activation map (right, red indicates early activation, purple late activation). Anatomical isthmus 3 between pulmonary valve (PV) and VSD-patch (grey dots) is marked with white brackets. B1: RV activation map demonstrates RV activation through a normal conducting anatomical isthmus 3 with fusion of the propagation wavefronts at the lateral tricuspid annulus (TA). B2: RV activation map demonstrates prolonged RV activation due to the localized

- conduction delay at anatomical isthmus 3 (i.e. slow conducting anatomical isthmus) causing a shift in the fusion site of activation wavefronts towards the RVOT. Panels C1-2 and D schematically illustrate the RV activation in presence of normal conducting anatomical isthmus 3 (C1) and slow conducting anatomical isthmus 3 (C2) causing a shift in RV fusion site (D) and QRS prolongation. PV, pulmonary valve; QRSd, QRS duration; RV, right ventricle; RVOT, RV outflow tract; vs, versus.

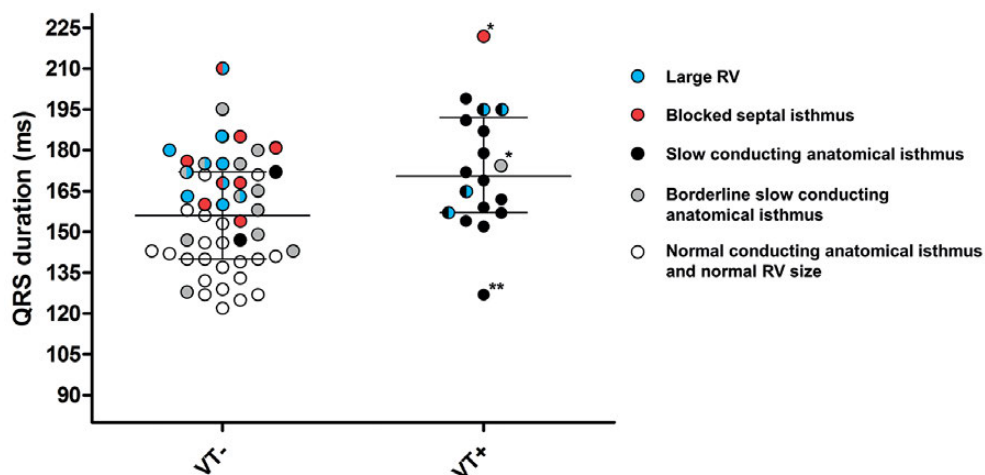


Figure 5. QRS duration according to VT inducibility and underlying mechanisms for QRS prolongation. Aligned dot plot. RV, right ventricle; VT, ventricular tachycardia; VT-, non-inducible for VT; VT+, inducible for VT; *, other VT substrates; **, patient with double septal isthmus (isthmus 3 with slow conduction and isthmus 4 with normal conduction velocity).

duration ≤ 150 ms had either a severely dilated RV or a blocked septal isthmus. These data suggest that in contemporary rTOF, a QRS duration between 120 and 150 ms is solely due to the postoperative RBBB.

The presence of RBBB with a QRS-duration > 150 ms was strongly associated with the presence of a slow conducting or blocked isthmus (OR 13.8 (95% CI, 2.9-66.2), $p=0.001$). After exclusion of patients with severely enlarged RV ($n=14$), the odds ratio of a QRS-duration > 150 ms for slow conducting or blocked AI was 16.6 (95% CI, 3.3- 84, $p=0.001$).

DISCUSSION

To the best of our knowledge, this is the first study using detailed 3D RV electroanatomical mapping to assess the relation between QRS duration, RV size and RV activation during SR and the substrate for reentry VT in patients with rTOF. We could demonstrate that rTOF patients with a narrow QRS can be at risk for life-threatening VT related to slow conducting anatomical isthmuses (SCAI). Rapid activation through the distal specific conduction system with fusion of wavefronts at the infundibulum can mask slow conduction in septal AIs. In these patients, the surface ECG does not contribute to substrate identification. In contrast, in rTOF

patients with a preexisting RBBB at any level, VT related SCAI further prolong the pathway for total RV activation resulting in QRS duration >150ms. A similar QRS prolongation in rTOF patients with RBBB but without SCAI can be observed in those with a severely dilated RV or with preexisting septal isthmus block. After exclusion of severe RV dilatation, a QRS duration >150ms is highly predictive for conduction delay at the infundibular septum as potential substrate for VT. To further distinguish between conduction delay within an AI as substrate for VT and conduction block requires electroanatomical mapping.

Ventricular arrhythmias and SCD in rTOF

Monomorphic VT (MVT) is the most common documented arrhythmia subtype in rTOF.^{6,7,14} Considering the typically short cycle length, MVTs may lead to SCD even if the biventricular function is preserved.^{4,5,24} Electroanatomical mapping studies have demonstrated that the dominant underlying mechanism of MVT is macro-reentry using SCAI located in the RVOT.^{14,23} In the present cohort, a SCAI was the substrate for all clinical and induced VTs in 22/24 patients.

QRS prolongation as risk factor for VT and SCD

A prolonged QRS duration has consistently been associated with both MVT and SCD in rTOF.⁸⁻¹⁰ In a large series of 182 patients, all 13 patients with (near-missed) SCD had QRS ≥ 180 ms, which was observed in only 5.3% of patients without an event. Of importance, all 9 SCD survivors underwent PES and were inducible for monomorphic fast reentry VT, suggesting that MVT had caused the event and that QRS prolongation may predict the substrate for reentry VT.⁹ PES performed in 134 unselected rTOF patients confirmed the association between QRS ≥ 180 ms and MVT. A QRS ≥ 180 ms was 35% sensitive and 97% specific for inducibility of any MVT and 100% sensitive and 96% specific for inducibility of the clinical VT.⁸ A subsequent multicenter study demonstrated that QRS ≥ 180 ms was the strongest independent predictor for VT with a remarkable HR of 41.9 (14.7-119.4).¹⁰ In more recent cohorts, the reported sensitivity of QRS ≥ 180 ms for death or VT was much lower (28%-53%) and a cutoff value of 170ms has been suggested (sensitivity 53%, specificity 86%).^{11,12} Similar, in our cohort QRS ≥ 180 ms was observed in only 6/24 (25%) patients with VT and in 7/54 (13%) without VT.

A modern transpulmonary approach may prevent a postoperative RBBB. As a consequence, an important number of contemporary rTOF patients has a narrow QRS without RBBB which may influence the predictive value of a prolonged QRS for VT/SCD if patients with and without RBBB are not separated. We could only demonstrate a significant difference in QRS duration between patients with and without VT after excluding the 11 (14%) rTOF patients with a narrow QRS. Of importance, the use of smaller transannular patches may reduce pulmonary valve regurgitation and RV dilatation. As a result, contemporary patients, with postoperative RBBB may still have less additional QRS prolongation, as the delayed myocardial activation of a severely dilated RV is avoided. Accordingly, in contemporary rTOF

patients with a postoperative RBBB, the optimal QRS cut-off for risk stratification needs to be redefined.

RV activation in rTOF patients with narrow QRS

All patients with narrow QRS showed early simultaneous RV activation at the anterior wall and the septum via distal ramifications of the conduction system with further propagation towards the anterolateral RVOT and the infundibular septum.²⁵ In the 6 patients with narrow QRS and isthmus related VT, fusion of activation wavefronts during SR was typically observed at the infundibular septum. Late activation after QRS offset was restricted to a small area with low bipolar voltages, therefore not contributing to the surface QRS. Such late potentials are also often observed in patients with scar related VTs of other etiologies. Of importance, in our series, a narrow QRS did not exclude a substrate for life-threatening VT. Although not performed in this study, signal averaged ECG (SAECG) may detect late activated infundibular regions with low voltages. Previous studies that have assessed the association between SAECG and ventricular arrhythmias were either performed in heterogeneous groups of patients with congenital heart disease or have looked at any ventricular arrhythmia, including PVCs and non-sustained VT as outcome parameter, with conflicting results.^{26, 27} One prior study conducted in 66 rTOF patients undergoing repair via a RV ventriculotomy with subsequent RBBB could demonstrate that patients who developed sustained VT (n=12, 18%) had a longer filtered QRS on SAECG compared to those without VTs (165 ± 17 ms versus 179 ± 18 ms, $p=0.01$).²⁸ Of interest, both additional SAECG criteria (RMS and HFLA), consistent with late activation of low amplitude regions, did not differ between groups. The predictive value of SAECG for sustained VT in contemporary rTOF patients with a narrow QRS has never been evaluated. Of interest, two patients with a narrow QRS had a severely dilated RV suggesting that in patients with rapid conduction through the specific conduction system rather than primary myocardial activation, RV size does not significantly contribute to QRS duration.

RV activation in rTOF patients with RBBB

In patients with RBBB, rapid conduction via the specific conduction system is interrupted and RV activation depends on slower myocardial impulse propagation. RBBB after surgery can be present at three levels; the proximal right fascicle, the distal ramification after infundibular resection or the peripheral conduction system secondary to the right ventriculotomy.²⁹ Of interest, a vertical ventriculotomy alone can result in a RBBB pattern with QRS prolongation by an average of 39ms.¹³ Irrespective of the level of block, the basal lateral RV and RVOT are activated late.²⁹ In our patients with RBBB and no additional area of conduction delay, the earliest RV activation during SR was always observed at the septum and excitation wavefronts were merging at the basal lateral tricuspid annulus. In patients with septal conduction delay due to SCAI or isthmus block, the pathway of impulse propagation was prolonged with a shift of latest activation towards the lateral RVOT. This latest area had

preserved voltage and contributed to prolongation of both the total RV activation time and QRS duration. This is in contrast to other forms of structural heart disease with scar related VT, where slow conduction within the scar results in late potentials of low amplitude inscribing after QRS offset.

QRS duration: global vs localized delay

In our series, all RBBB patients had normal CV remote from the anatomically defined isthmuses (i.e. normal global CV). Despite normal global CV, severe RV dilation can also prolong the pathway for myocardial impulse propagation leading to an increase in QRS duration. Fourteen of the 44 RBBB patients with QRS >150ms had a severely enlarged RV. In 8/14 QRS prolongation was solely due to longer RV activation time of the dilated RV, in 6/14 patients a SCAI or isthmus block further contributed to QRS prolongation. This data supports that local rather global myocardial conduction delay or block contributes to QRS prolongation in the majority of patients. The localized conduction delay or isthmus block resulted in a shift of latest activation towards the RVOT. The observed shift in latest activation provides a potential explanation for prior findings on right ventricular dyssynchrony showing that QRS duration was strongly associated with the delay in RVOT shortening, which was more pronounced if QRS was ≥ 155 ms. The delay increased to more than the upper 95% in all pts with a QRS >165ms.³⁰

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The link between QRS duration and VT in rTOF

According to our data, in the absence of a severely enlarged RV, a QRS >150ms is highly suspicious for the presence of a SCAI as potential substrate for VT. This finding provides an important link between prolonged QRS and VT substrate in rTOF patients with RBBB. In only one patient of our cohort, the VT substrate, i.e. the SCAI, did not influence QRS duration because of the presence of a second and normal conducting septal isthmus. A QRS>150ms can also be observed in patients with preexisting isthmus block. Information on isthmus block can be sometimes derived from the operation records, e.g. description of an absent infundibular septum. If not conclusive, EAM is required to distinguish slow conduction as substrate for VT from pre-existing block.

LIMITATIONS

This study is limited by the cross-sectional-design. In the current study, rTOF patients who were considered at risk for VT or who presented with spontaneous VT underwent PES with RV mapping. The results can therefore not be applied to the general rTOF population. In 5 patients with a RBBB, we could not identify the mechanism of QRS >150ms. As electroanatomical CV was measured only at the endocardium and not at the epicardium, additional epicardial and transmural conduction delay cannot be excluded. In addition, a large RV was predefined based on one RVEDVi cut off value.

CONCLUSION

In rTOF with pre-existing RBBB, the increased QRS duration is frequently due to localized conduction delay across the AI rather the global delay. These SCAIs prolong the pathway for RV activation and QRS duration providing an important causal link between QRS width and substrate for VT. After exclusion of severe RV dilatation, a QRS >150ms is highly predictive for a SCAI and may justify electroanatomical mapping to distinguish between a slow conducting and blocked AI. A narrow QRS in rTOF patients does not exclude SCAI and the risk for VT.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge

The dominant substrate for ventricular tachycardia (VT) in repaired Tetralogy of Fallot (rTOF) are slow conducting anatomical isthmuses (SCAI). In rTOF patients with right bundle branch block (RBBB), SCAI increase RV activation time and QRS duration. In rTOF patients with a narrow QRS, SCAI does not influence QRS duration.

Competency in Patient Care 1

In rTOF patients with RBBB, a QRS duration >150ms is highly suggestive for presence of a SCAI or blocked isthmus, in particular in patients without severe RV dilatation. Electroanatomical mapping can distinguish SCAI from isthmus block and may become an important tool for VT substrate identification.

Competency in Patient Care 2

In repaired TOF patients with a narrow QRS, a VT substrate cannot be excluded.

Translational Outlook

Data are based on a cross-sectional study in a selected group of rTOF patients with documented sustained VT, considered at risk for VT and/or with indication for re-operation. Further studies in the contemporary rTOF population are desirable.

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SUPPLEMENT – METHODS

1. LEADS

LEADS (Leiden ECG Analysis and Decomposition Software) is a MATLAB based computer program. LEADS automatically detects all QRS complexes of a 12 lead ECG based on signal-to-noise ratio, on interbeat interval time and QRS-T morphology. After the automated beat selection, each individual beat is reviewed by the analyst who can optimize beat selection. The selected beats are then averaged into a single QRS complex, subsequently QRS duration can be measured with high accuracy.

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2. Induction protocol.

Induction protocol was performed at ≥ 2 right ventricular (RV) sites, always including RV-apex and RV outflow tract (RVOT) close to the infundibular septum, using three drive cycle lengths (400, 500 and 600ms) with up to three extra stimuli down to refractoriness before and during isoproterenol infusion (2-10 μ g/min).

3. Electroanatomical identification of the anatomical isthmuses.

During RV mapping, high out pacing (≥ 10 mA, 2ms) was performed at low voltage sites (< 1.5 mV) to identify electrically unexcitable tissue (patches and surgical scars), which together with the tricuspid annulus and pulmonary valve form the boundaries of the four potential anatomical isthmuses.

4. Non-anatomical isthmus conduction velocity (CV) measurement.

To compare CV within and remote from the anatomically defined isthmuses, CV was calculated for three additional RV areas remote from the anatomical isthmuses: RV septum, RV free wall and RV outflow tract free wall. For this purpose, the RV activation maps during sinus rhythm were displayed as isochronal maps and the CV was calculated in the direction of the endocardial propagation wave front. CV measurements were performed at ≥ 3 sites/area and averaged per area. Non-anatomical isthmus CV was defined as the average of all CV.

SUPPLEMENT – RESULTS

1. VT related substrates

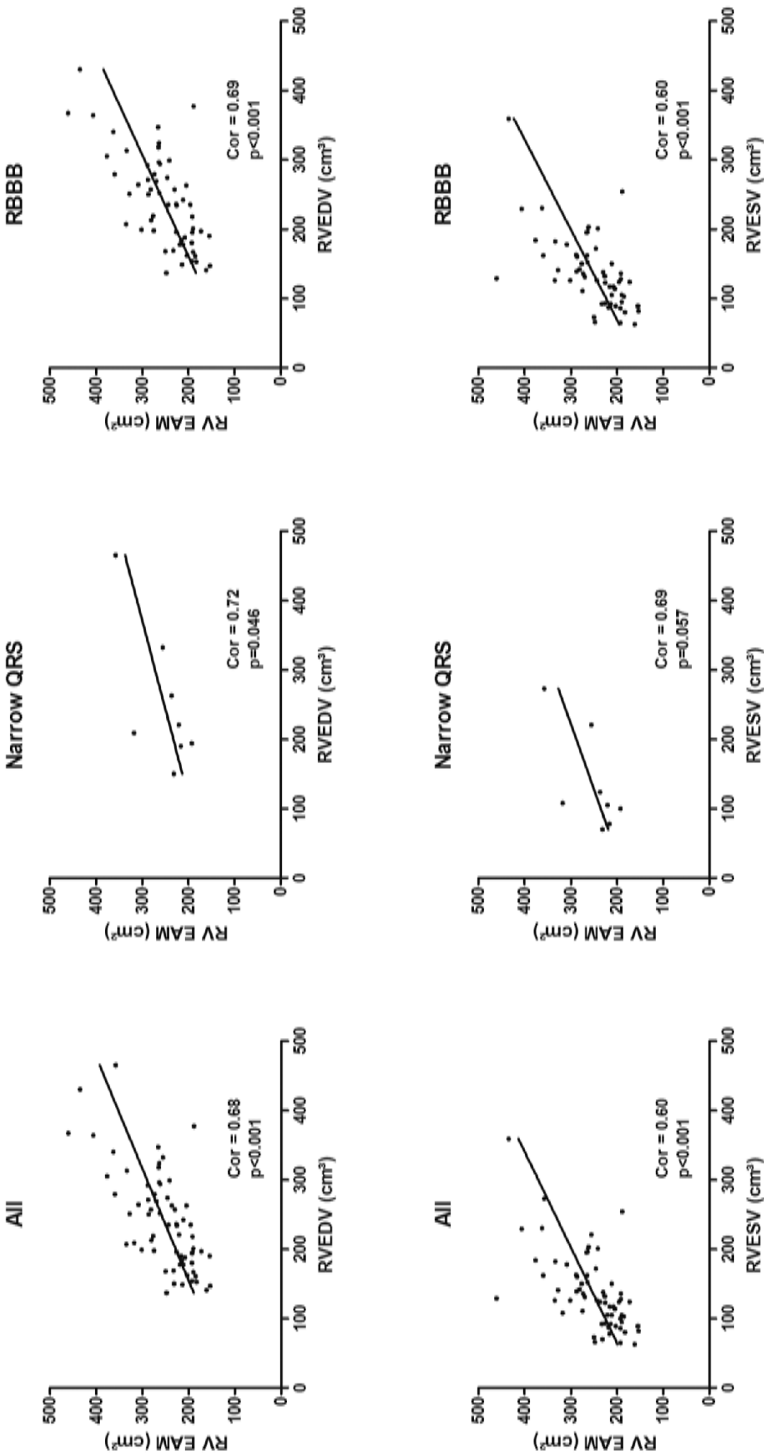
A total of 34 VTs were induced. Thirty-two of the 34 VTs were related to a SCAI. The 2 remaining VT that were not related to a SCAI were observed in 2 patients with advanced heart failure and poor RV function, 1 VT was related to a large free wall scar and 1 VT was due to a focal VT mechanism. Participation of a SCAI in the VT circuit was based on pace-mapping in 22 (due to the fast and hemodynamically not tolerated VT), entrainment mapping in 3 and 7 VTs were related to a SCAI based on diastolic activity during VT with VT termination by RF-delivery.

2. Acute and long-term VT ablation outcome data

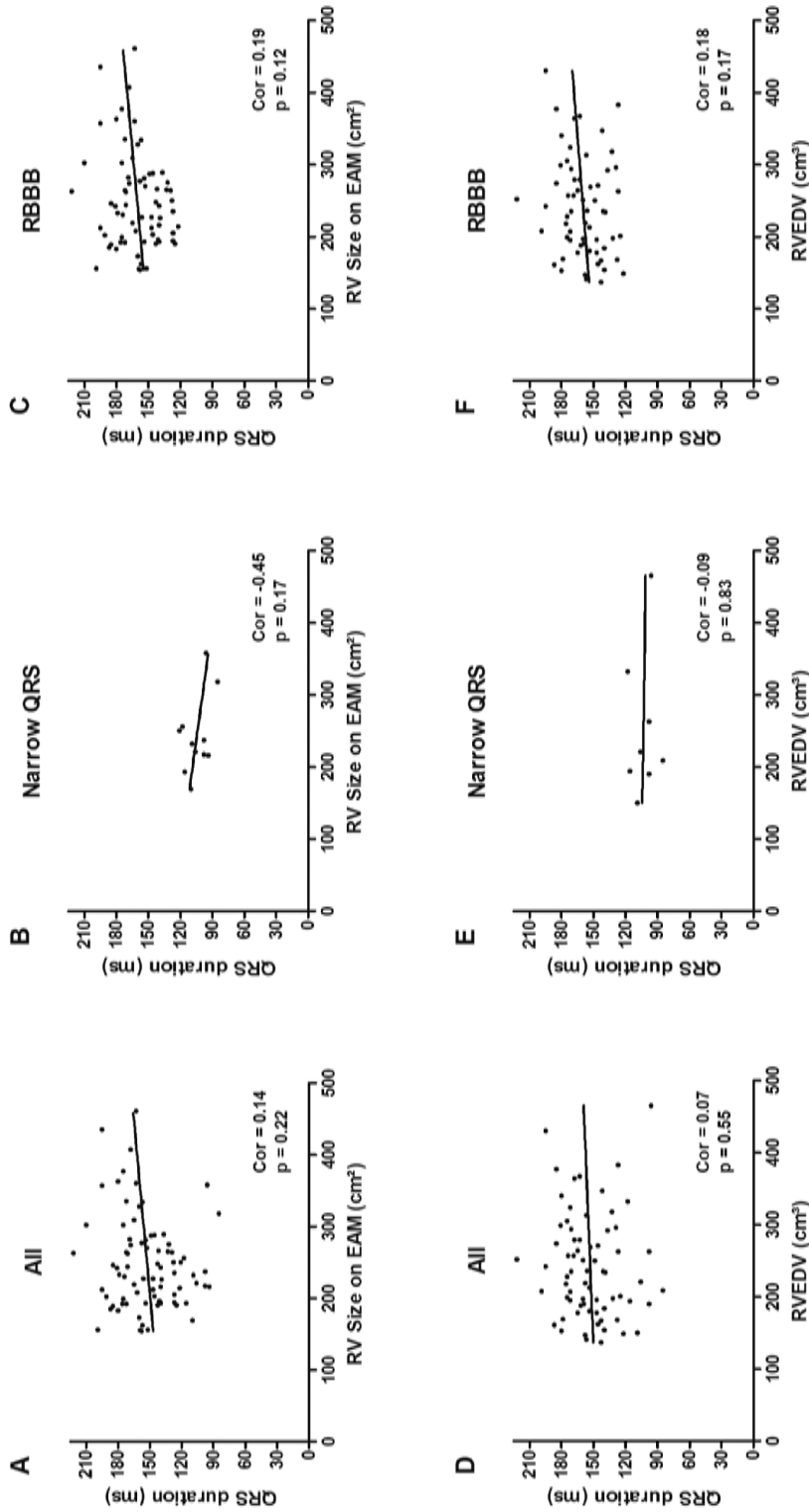
A total of 24 patients were inducible for VT. Twenty-two of these 24 patients had VT related to a SCAI and 14 of these 22 patients underwent successful ablation. Another two patients had SCAI, but were not inducible for VT. Both of these two patients underwent successful ablation, defined as bidirectional block of the SCAI. In addition, 52 patients had no SCAI and were not inducible for VT. All 68 patients without a SCAI (52 at baseline and 16 after successful SCAI ablation) remained free from VT during long-term follow-up (39 ± 24 months). Eight patients with SCAI related VT had a SCAI during follow-up due to failed ablation ($n=6$) or no ablation ($n=2$). Four of these 8 patients experienced VT during long-term follow-up (35 ± 19 months, $p < 0.001$). In addition, there were two patients with VT that was not related to a SCAI, one of these 2 patients underwent successful VT ablation and VT ablation failed in the other patient.

SUPPLEMENT – ONLINE FIGURES

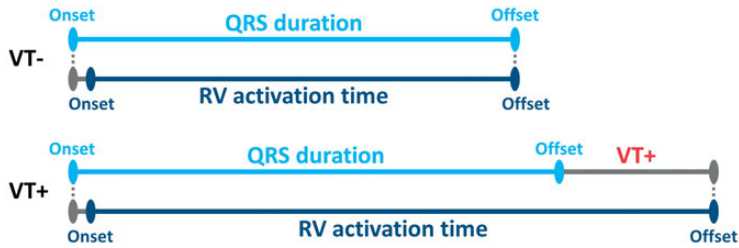
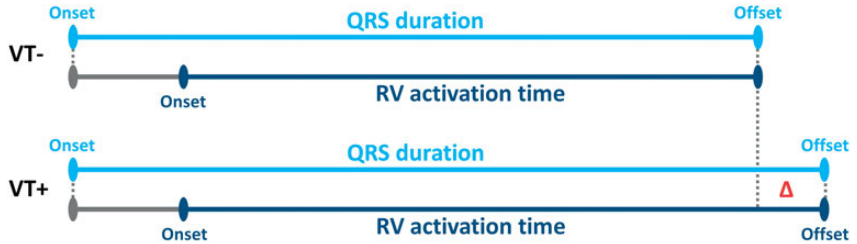
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Online figure 1. Scatterplots A-C: Relation between RV size on electroanatomical map and RV end diastolic volume on CMR for all patients (A), patients with narrow QRS (B) and with RBBB (C). Scatterplots D-F: Relation between RV size on the electroanatomical map and RV end systolic volume on CMR for all patients (D), patients with narrow QRS (E) and with RBBB (F). CMR, cardiac magnetic resonance imaging; Cor, correlation; EAM, electroanatomical map; RBBB, right bundle branch block; RV, right ventricle; RVEDV, RV end diastolic volume; RVESV, RV end systolic volume.



Online figure 2. Scatterplots A-C: Relation between RV size on the electroanatomical map and QRS duration for all patients (A), patients with narrow QRS (B) and with RBBB (C). Scatterplots D-F: Relation between RV end diastolic volume on CMR and QRS duration for all patients (D), patients with narrow QRS (E) and with RBBB (F). CMR, cardiac magnetic resonance imaging; Cor, correlation; EAM, electroanatomical map; RBBB, right bundle branch block; RV, right ventricle; RVEDV, RV end diastolic volume.

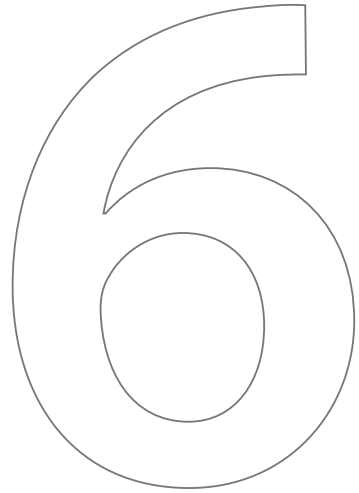
Non-RBBB**RBBB**

Online figure 3. Schematic overview to demonstrate key similarities and differences in QRS duration and RV activation time between patients with and without VT in absence (non-RBBB) or presence of RBBB. Non-RBBB patients with VT show RV activation after QRS-offset, which is not observed in non-RBBB patients without VT. In non-RBBB patients with VT, parts of the VT substrate (red, VT+) are activated after QRS-offset, but not contributing to the 12-lead ECG. RBBB patients with VT have a significantly longer (red Δ) QRS duration and RV activation time than those without VT. Both in patients with and without VT, RV activation starts after QRS-onset and ends with the QRS-offset. RBBB, right bundle branch block; RV, right ventricle; VT, ventricular tachycardia; VT -, not inducible for VT; VT+, inducible for VT; Δ, difference.

SUPPLEMENT - VIDEO LEGEND

Video 1: A right ventricular (RV) electroanatomical activation map showing propagation during sinus rhythm of a rTOF patient with right bundle branch block and with *normal conducting anatomical isthmuses*. The earliest activation can be observed in a broad area at the mid to basal RV septum. The activation propagates in different wavefronts through the septal anatomical isthmus and non-septal anatomical isthmus, across the inferior wall *and* across the RV free wall with fusion of the wavefronts at the basal *lateral tricuspid annulus*.

Video 2: A right ventricular (RV) electroanatomical activation map showing propagation during sinus rhythm of a rTOF patient with right bundle branch block and VT related to *a slow conducting septal anatomical isthmus* between the ventricular septal defect patch and the pulmonary valve. The earliest activation can be observed in a broad area at the mid to basal RV septum. The activation propagates in different wave fronts through the septal anatomical isthmus, across the inferior wall *and* across the RV free wall. The delay at the septal anatomical isthmus results in a shift of fusion of wavefronts towards the *lateral right ventricular outflow tract*, which prolongs the pathway for RV activation and QRS duration.



The Impact of Surgery on Presence and Dimensions of Anatomical Isthmuses in Tetralogy of Fallot

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Published: Heart, 5th of January 2018 (electronic publication ahead of print)

ABSTRACT

Objective

In Tetralogy of Fallot (TOF), the dominant ventricular tachycardia (VT) substrate are slow conducting anatomical isthmuses. Surgical correction has evolved, which might have influenced isthmus presence and dimensions.

Methods

One-hundred-forty-two post-mortem TOF specimens (84/58 corrected/uncorrected) were studied for isthmus presence. Isthmus 1 is located between the tricuspid annulus and right ventricular (RV) outflow tract (RVOT)-patch/RV-incision, Isthmus 2 between RVOT-patch/RV-incision and pulmonary valve, Isthmus 3 between pulmonary valve and ventricular septal defect (patch), Isthmus 4 between ventricular septal defect (patch) and tricuspid annulus. Isthmus width and thickness were measured.

Results

Of 84 corrected post-mortem TOF specimens (death: 6.6 years (4.0-11.5)) 83 demonstrated Isthmus 1 (99%, width= 25 ± 10 mm, thickness= 5 ± 2 mm), 35 Isthmus 2 (42%, width= 10 ± 9 mm, thickness= 3 ± 2 mm), 83 Isthmus 3 (99%, width= 10 ± 6 mm, thickness= 5 ± 2 mm), and 5 Isthmus 4 (6%, width= 4 ± 2 mm, thickness= 2 ± 1 mm). Transatrial-transpulmonary correction (n=49) as compared to transventricular correction (n=35) prevented Isthmus 2 (0% versus 100%, $p<0.001$). Transatrial-transpulmonary correction at age <1 year (n=7) as compared to ≥ 1 year (n=42) required a smaller transannular RVOT-patch (28 ± 15 versus 45 ± 14 mm, $p<0.001$). Mode and timing of correction did not influence presence and dimensions of Isthmus 3. In corrected and uncorrected TOF specimens (death 1.8 years (0.5-6.6)), the range of Isthmus 3 dimensions was broad (width: min=2mm, max=32mm; thickness: min=1, max 13mm) across all ages. Isthmus 3 width and thickness were strongly correlated ($r=0.65$, $p<0.001$).

Conclusions

In TOF, the current routine use of transatrial-transpulmonary correction prevents Isthmus 2. Correction <1 year reduces transannular-patch size, which may influence Isthmus 1 width later in life. Mode and timing of correction did not change prevalence and dimensions of Isthmus 3, which dimensions varied widely in uncorrected and corrected TOF.

INTRODUCTION

Tetralogy of Fallot (TOF) is the most prevalent cyanotic congenital heart disease.¹ The population of adults with corrected TOF is progressively growing due to improved surgical techniques extending survival.^{1, 2} Late morbidity and mortality in TOF are often caused by ventricular arrhythmias (VA).^{3, 4} The majority of VA are monomorphic re-entrant ventricular tachycardias (VTs).⁵ The dominant substrate for these re-entrant monomorphic VTs are slow conducting anatomical isthmuses located in the right ventricular (RV) outflow tract (RVOT).⁶⁻⁸ Anatomical isthmuses with slow conduction are significantly narrower as compared to anatomical isthmuses without slow conduction.⁷

Presence and dimensions, i.e. width and thickness, of the isthmuses are the result of both the anatomical features of the malformation itself and of the surgical correction. Surgical techniques have evolved over time. Nowadays, surgeons preferably use a transatrial-transpulmonary approach instead of the transventricular approach.⁹ In addition, the timing of repair has shifted from the first decade of life to the first year of life.¹⁰ The aim of the current study was twofold (1) to assess the presence and dimensions of the isthmuses according to mode and timing of correction in post-mortem TOF specimens, (2) to gain insight into the natural growth and the effect of correction of the isthmus between the pulmonary valve (PV) and ventricular septal defect (VSD). This isthmus, that is part of the malformation itself, is the most prevalent arrhythmogenic isthmus in TOF.^{6, 7}

Methods

Specimen selection

This study was undertaken in accordance with the local ethics committee and the Dutch regulation for the proper use of human tissue for medical research purposes. The Leiden Collection of malformed hearts (Department of Anatomy and Embryology, Leiden University Medical Centre, Leiden, The Netherlands), a collection consisting of hearts preserved in ethanol and glycerine dating from the nineteen fifties to the present era, was reviewed for corrected and uncorrected TOF hearts. The anatomical spectrum of TOF phenotype is broad; in the current study specimens with 'classical' TOF and TOF with double outlet ventricle (DORV, defined as >50% overriding of the aortic annulus over the ventricular septum) were included. Specimens with sub-aortic VSD with valvular/muscular pulmonary atresia, concomitant atrioventricular septal defect and hearts too damaged to be analysed were excluded from the analysis. A total of 142 TOF hearts were included.

Specimens characteristics (clinical data)

The (anonymized) medical records of the 84 corrected and 58 uncorrected patients from whom the specimens were obtained between 1950 and 2007, were reviewed for age, gender, palliative surgery, corrective surgery and mode of death. If palliative surgery was performed, the following data was collected: date and type, i.e. Brock (dilatation of the PV/membranous valvular atresia), Potts shunt (descending aorta-left pulmonary artery), Waterston shunt

(ascending aorta-right pulmonary artery) or Blalock Taussig shunt (subclavian artery-pulmonary artery). If correction was performed, the following data was collected: date and mode, i.e. transannular RVOT-patch/incision, non-transannular RV-incision/patch, VSD closure and infundibular resection.

Specimen measurements

All included specimens, if corrective surgery was performed, were visually assessed for mode of correction, i.e. transannular RVOT-patch (including size) or RV-incision, non-transannular RV-incision/patch, VSD closure and infundibular resection. If a discrepancy was present between operation reports and visual assessment, visual assessment determined the definitive classification. The transventricular approach was defined by a ventriculotomy into the RV myocardial wall remote from the PV. The transatrial-transpulmonary approach was defined by correction via the tricuspid valve and/or PV and, if required, division of the pulmonary annulus with a limited ventriculotomy extended from the valve annulus and reconstructed by a transannular patch.¹¹

All included specimens were assessed for the presence of the four potential isthmuses (Figure 1).^{6,8} The first potential isthmus is bordered by the tricuspid annulus and a RVOT-patch or RV-incision, the second potential isthmus is bordered by the PV and a non-transannular RV-incision/patch, the third potential isthmus is bordered by the VSD-patch and PV, and the fourth potential isthmus is bordered by the VSD-patch and the tricuspid annulus (only present in case of a VSD with muscular postero-inferior rim, i.e. non-perimembraneous VSD). Isthmus 1 and 2 are the result of the correction, therefore only assessed in corrected specimens. Isthmus 3 and 4 are due to the malformation, therefore assessed in all specimens.

The width and thickness of the identified isthmuses were measured (Figure 1). Isthmus width was defined as the shortest distance between the two bordering anatomical structures, e.g. the shortest distance between the PV and VSD(-patch) in case of isthmus 3. The thickness of the isthmuses was assessed using a straight biceps with a built-in calliper. If isthmus thickness could not be assessed with a straight biceps due to anatomical reasons, e.g. closed VSD, a curved biceps with calliper was used. The size of the RV was defined as the shortest distance between the RV apex and the PV (to include the RVOT). Isthmus dimensions (width and thickness) were corrected for RV size.

Statistical analysis

Continuous data are reported as mean±standard deviation (SD) or median with inter quartile range (IQR) according to data distribution. Categorical data are presented as frequencies or percentages. In case of two groups, groups were compared using a student's T-test, Mann-Whitney U test or Chi-Square test where appropriate. TOF specimens corrected with a transventricular approach were compared to TOF specimens corrected with a transatrial-transpulmonary approach. Furthermore, TOF specimens with a transatrial-transpulmonary correction <1 year of age were compared TOF specimens with a transatrial-transpulmonary correction ≥1 year. To compare isthmus dimensions between these two age groups, isthmus

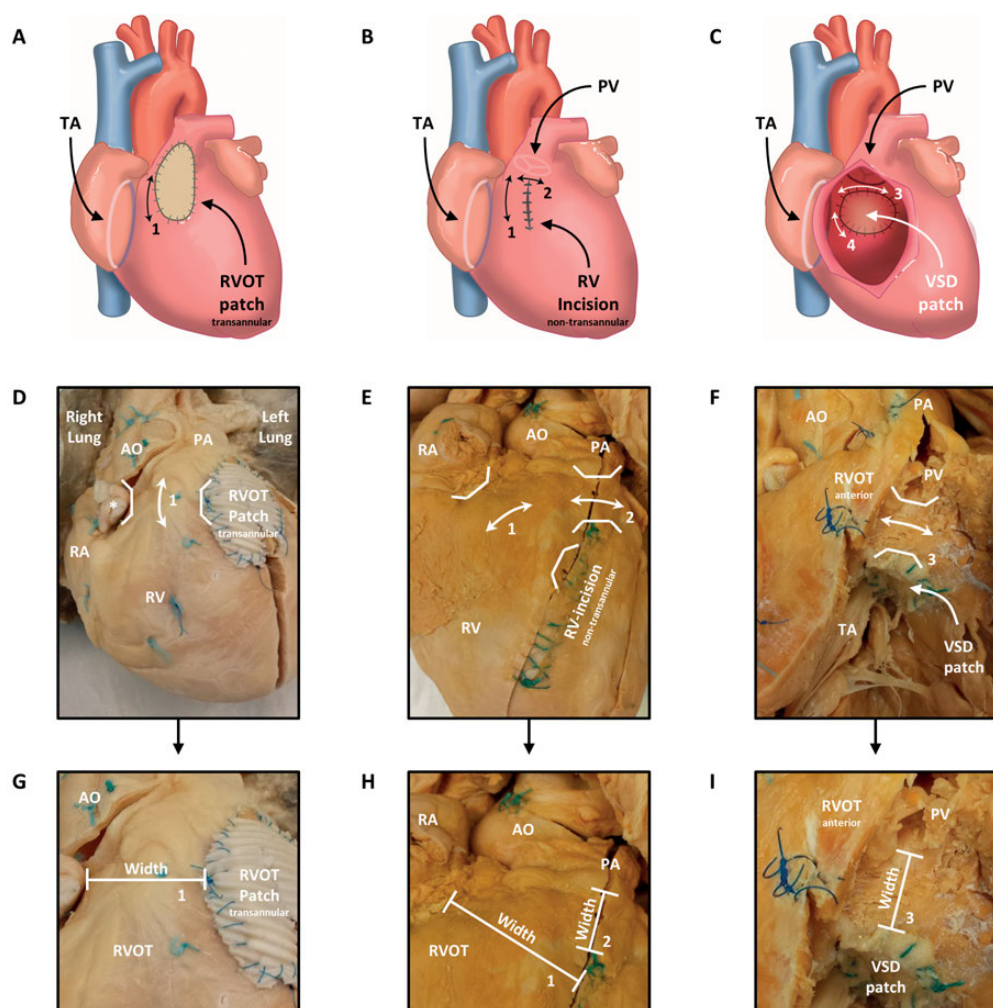


Figure 1. Overview of anatomical isthmuses. Panel A-C: Schematic overview of anatomical isthmuses: isthmus 1 between tricuspid annulus (TA) and right ventricular (RV) outflow tract (RVOT) patch / RV-incision, isthmus 2 between non-transannular RV-incision and pulmonary valve (PV), isthmus 3 between ventricular septal defect (VSD) patch and PV, isthmus 4 between VSD-patch and TA. Panel D-F: Anatomical specimens with isthmus 1, 2 and 3 (F: isthmus 4 absent, because of non-muscular VSD). Panel G-I: RVOT in detail of panel D-F, illustrating isthmus width. AO, aorta; PA, pulmonary artery; RA, right atrium; *, RA appendage.

size was adjusted for RV size if an association was present based on Pearson correlation. Uncorrected and corrected TOF specimens were compared for isthmus 3 width and thickness. In addition, the associations between (i) isthmus 3 width and age, (ii) isthmus 3 thickness and age, and (iii) isthmus 3 width and thickness were illustrated with scatterplots for (un) corrected TOF specimens and were evaluated by Pearson correlation. A p-value <0.05 were considered statistically significant. SPSS software (20.0, SPSS Inc, Chicago, USA) was used.

RESULTS

Corrected specimens: Patient characteristics

The cohort consisted of 84 corrected patients (60% male). The median age was 6.6 (4.0–11.5) years, the youngest age was 1 month, 20 patients (24%) were ≥ 12 years, the oldest patient was 57 years (Table 1, Figure 2). RV size was 64 ± 17 mm. Thirty-two TOF patients (38%) also had DORV. Thirty-nine (46%) patients (median age 3.0 years (1.4–4.9)) underwent palliative surgery before correction, details are provided in Supplement A1. Patients were corrected at median age of 6.5 years (4.0–10.5) with a transannular RVOT-patch/incision in 63% of patients (n=53) and with a non-transannular RV-incision/patch in 42% of patients (n=35). Of these

Table 1. Corrected specimens: Baseline characteristics.

	All corrected patients (n=84)	Transventricular correction (n=35)	Transatrial-transpulmonary correction (n=49)	p
Age (y)	6.6 (4.0–11.5)	7.7 (4.8–14.4)	6.4 (2.0–8.8)	0.053
Age category (y)				
<1	8 (10%)	1 (3%)	7 (14%)	0.249
1 - <4	13 (16%)	3 (9%)	10 (20%)	
4 - <8	29 (35%)	14 (40%)	15 (31%)	
8 - <12	14 (17%)	6 (17%)	8 (16%)	
12 - <18	11 (13%)	6 (17%)	5 (10%)	
18 or older	9 (11%)	5 (14%)	4 (8%)	
Gender (male)	50 (60%)	24 (69%)	26 (53%)	0.153
RV size (mm)	64 ± 17	65 ± 14	62 ± 19	0.444
DORV	32 (38%)	13 (37%)	19 (39%)	0.879
Correction				
Year	70 ('63-'74)	69 ('64-'71)	71 ('63-'77)	0.120
Age (y)	6.5 (4.0–10.5)	7.7 (4.8–14.3)	6.4 (2.0–8.3)	0.023
TA: RVOT-patch or incision	53 (63%)	5 (14%)	48 (98%)	<0.001
Transannular RVOT-patch	52 (62%)	5 (14%)	47 (96%)	<0.001
Transannular RVOT-incision	1 (1%)	0 (0%)	1 (2%)	0.099
Non-TA: RVOT-patch or incision	35 (42%)	35 (100%)	0 (0%)	<0.001
Non-transannular RVOT-patch	4 (5%)	4 (11%)	0 (0%)	0.015
Non-transannular RVOT-incision	31 (37%)	31 (89%)	0 (0%)	<0.001
Infundibular resection	76/82* (93%)	33 (94%)	43/47* (92%)	0.631
Death				
Death perioperative	78 (93%)	34 (97%)	44 (90%)	0.197
Cardiac, all	50/68* (74%)	23/31* (74%)	27/37* (73%)	0.910
Death non-perioperative	6 (7%)	1 (3%)	5 (10%)	
Cardiac	3/4* (75%)	1 (100%)	2/3* (67%)	0.505
Time from correction to death (y)	0.4 (0.2–17.1)	0.4	0.4 (0.1–22.8)	1.000

DORV, double outlet RV; mm, millimeter; OT, outflow tract; RV, right ventricle; TA, transannular; y, year; *, missing data.

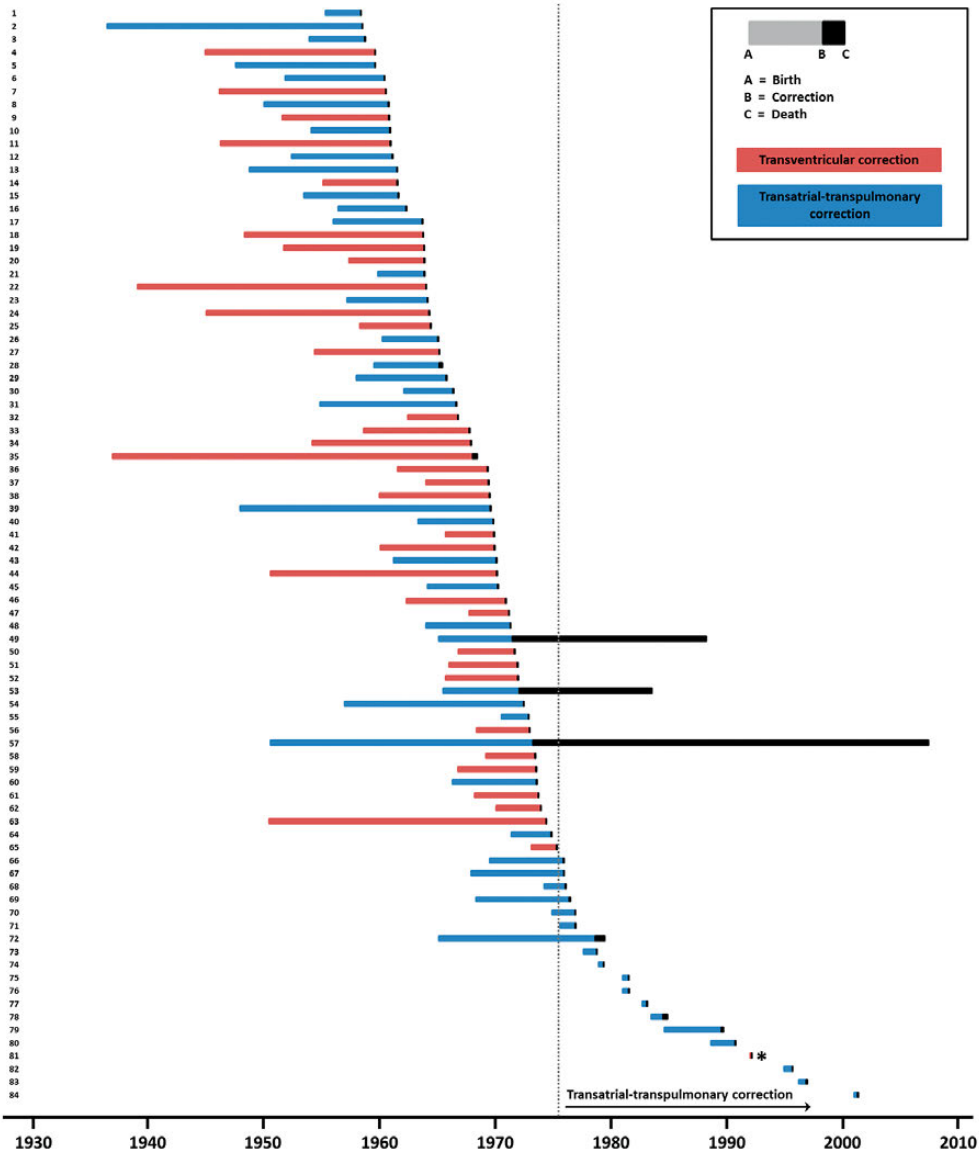


Figure 2. Overview of age, timing of correction and survival after correction of 84 corrected patients between 1936 and 2007 covering a period of 81 years, according to mode of correction. After 1975, all patients underwent transatrial-transpulmonary correction, except for one patient (number 81, marked with *) that underwent transventricular correction due to major coronary aberrancy (supplement A2).

patients, 5 had a transannular RVOT-patch/incision as well as a separate non-transannular RV-incision/patch. Seventy-eight patients (93%) died during the perioperative period (Figure 2), from cardiac causes in 74% of the cases. The remaining six patients died a median of 0.4 years (0.2–17.1) years after correction, from cardiac causes in 75% of the cases.

Thirty-five patients (42%) were corrected with a transventricular approach and 49 patients (58%) were corrected with transatrial-transpulmonary approach. Patients with a transatrial-transpulmonary approach were corrected at younger age as compared to patients with a transventricular approach (6.4 (2.0–8.3) versus 7.7 (4.8–14.3) years, $p=0.023$) and more often with the use of a transannular RVOT-patch (96% versus 14%, $p<0.001$).

Corrected specimens: the influence of mode of correction

Isthmus 1, the isthmus between tricuspid annulus and RV-incision/RVOT-patch, and isthmus 3, the isthmus between PV and VSD-patch, were both present in 99% of the patients ($n=83$) (Table 2). Isthmus 2, the isthmus between the PV and a non-transannular RV-incision/patch was present in 35 patients (42%). Isthmus 4, the isthmus between the tricuspid valve and VSD-patch (in cases with a non-perimembraneous VSD), was present in only 5 patients (6%). The width and thickness of isthmus 1, 2, 3 and 4 were respectively 25 ± 10 by 5 ± 2 mm, 10 ± 9 by 3 ± 2 mm, 10 ± 6 by 5 ± 2 mm and 4 ± 2 by 2 ± 1 mm (Table 2).

There was no difference in presence of isthmus 1, 3 and 4 between both modes of correction. However, isthmus 2 was present in all 35 patients with a transventricular correction and absent in all 49 patients with a transatrial-transpulmonary correction ($p<0.001$). Of interest, in our cohort, the transventricular correction was no longer observed after July 1975 except for in 1 patient (Figure 2 – patient 81). This patient had an isolated RV-patch

Table 2. Corrected specimens: Isthmus presence and properties.

	All corrected patients (n=84)	Transventricular correction (n=35)	Transatrial-transpulmonary correction (n=49)	p
Isthmus 1				
Present (n)	83 (99%)	35 (100%)	48 (98%)	0.395
Width (mm)	25 ± 10	27 ± 9	23 ± 9	0.122
Thickness (mm)	5 ± 2	5 ± 2	6 ± 2	0.036
Isthmus 2				
Present (n)	35 (42%)	35 (100%)	0 (0%)	<0.001
Width (mm)	10 ± 9	10 ± 9		
Thickness (mm)	3 ± 2	3 ± 2		
Isthmus 3				
Present (n)	83 (99%)	34 (97%)	49 (100%)	0.234
Width (mm)	10 ± 6	10 ± 5	10 ± 7	0.489
Thickness (mm)	5 ± 2	5 ± 2	5 ± 3	0.666
Isthmus 4				
Present (n)	5 (6%)	2 (6%)	3 (6%)	0.938
Width (mm)	4 ± 2	4 ± 1	4 ± 3	1.000
Thickness (mm)	2 ± 1	3 ± 1	2 ± 1	0.333

Mm, millimeter.

due to aberrant coronary anatomy (LAD from RCA, crossing the anterior RVOT just below the PV (Supplement A2)). Thus, after 1975, TOF patients without major coronary aberrancy underwent transatrial-transpulmonary correction and subsequently isthmus 2 was no longer encountered. Dimensions of isthmus 3 and 4 did not differ between both modes of correction. However, isthmus 1 was significantly thicker in patients with a transatrial-transpulmonary approach ($p=0.036$).

Corrected specimens: the influence of timing using the transatrial-transpulmonary correction

In the 49 TOF patients corrected with a transatrial-transpulmonary approach, isthmus 1, 3 and 4 were present in 98%, 100% and 6% of the patients and a transannular RVOT-patch (size $43\pm 15\text{mm}$) was used in 47 patients (96%). In these 49 patients, width and thickness of isthmus 1, 3 and 4 were 23 ± 9 by $6\pm 2\text{mm}$, 10 ± 7 by $5\pm 3\text{mm}$ and 4 ± 3 by $2\pm 1\text{mm}$ respectively (Table 3). Width of isthmus 1 and 3 was associated with RV-size ($r=0.67$, $p<0.001$ and $r=0.34$, $p<0.018$).

Of interest, the transannular RVOT-patch was 1.6 times smaller in the 7 patients corrected with a transatrial-transpulmonary approach below the age of 1 year ($28\pm 15\text{mm}$) as compared

Table 3. Corrected specimens: Isthmus properties after transatrial-transpulmonary correction according to timing of correction.

	Transatrial-transpulmonary correction (n=49)	Correction <1 year (n=7)	Correction ≥ 1 year (n=42)	p
Isthmus 1				
Present (n)	48 (98%)	6 (86%)	42 (100%)	0.013
TA-patch (size)	43 ± 15	28 ± 15	45 ± 14	0.009
Width (mm)	23 ± 9	15 ± 2	24 ± 9	<0.001
Width (mm) / RV-size (mm)	0.37 ± 0.10	0.41 ± 0.05	0.37 ± 0.10	0.190
Thickness (mm)	6 ± 2	5 ± 1	6 ± 2	0.553
Isthmus 3				
Present (n)	49 (100%)	7 (100%)	42 (100%)	1.000
Width (mm)	10 ± 7	5 ± 2	11 ± 7	0.013
Width (mm) / RV-size (mm)	0.16 ± 0.08	0.15 ± 0.06	0.16 ± 0.09	1.000
Thickness (mm)	5 ± 3	3 ± 2	5 ± 3	0.108
Isthmus 4				
Present (n)	3 (6%)	0 (0%)	3 (7%)	0.466
Width (mm)	4 ± 3		4 ± 3	
Thickness (mm)	2 ± 1		2 ± 1	
RV size (mm)	62 ± 19	37 ± 4	67 ± 16	<0.001

Mm, millimeter; RV, right ventricle; TA, transannular.

to the 42 patients corrected with a transatrial-transpulmonary approach above the age of 1 year (45 ± 14 mm, $p=0.009$). There was no difference in presence and dimensions of isthmus 3 between patients corrected with a transatrial-transpulmonary approach below the age of 1 year and ≥ 1 year (Table 3).

Uncorrected specimens: baseline characteristics

The cohort consisted of 58 uncorrected TOF patients (68% male, 33% DORV) with a median age of 1.8 (0.5–6.6) years, 6 patients (10%) were >12 years old and the oldest patient was 78 years. The RV size was 52 ± 19 mm. Palliative operations and mode of death are described in table 4. Isthmus 3 was present in 55 patients (95%), 10 ± 6 mm broad and 5 ± 3 mm thick.

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Uncorrected versus corrected specimens

The 58 patients with uncorrected TOF were significantly younger as compared to the 84 patients with corrected TOF (1.8 (0.5–6.6) years versus 6.6 (4.0–11.5) years, $p<0.001$). There was no statistical significant difference between uncorrected and corrected specimens in

Table 4. Uncorrected patients: Baseline characteristics.

	All (n=58)
Age (y)	1.8 (0.5-6.6)
Age category (y)	
<1	23 (40%)
1 - <4	17 (29%)
4 - <8	5 (9%)
8 - <12	7 (12%)
12 - <18	2 (3%)
18 or older	4 (7%)
Gender (male)	39/57* (68%)
DORV	19 (33%)
RV size	52 ± 19
Palliative operation	
Age	2.0 (0.6-6.2)
Year	63 ('57-'69)
Type	
Brock	9 (24%)
Swan	2 (5%)
Shunt - Potts	4 (11%)
Shunt - Waterston	9 (24%)
Shunt - Blalock Tausig	13 (34%)
Death	
Death perioperative	37/54* (69%)
Death non-perioperative	17/54* (31%)

DORV, double outlet RV; mm, millimeter; RV, right ventricle; y, year; *, missing data.

isthmus 3 presence and dimensions. However, this may be partly due to the differences in age distribution. For the age subgroups isthmus 3 tended to be wider beyond the age of 1 in uncorrected specimens, Table 5. Of importance, the range of isthmus 3 width (min - max: 2 – 32mm) and thickness (min – max: 1 – 13mm) was very large across all ages for both corrected and uncorrected patients (Figure 3A-D) and was associated with age (respectively $r=0.34$, $p<0.001$ and $r=0.24$, $p=0.005$). Furthermore, there was a significant correlation between isthmus 3 width and thickness ($r=0.65$, $p<0.001$). Thus, a narrow isthmus 3 in TOF specimens are likely to contain thinner myocardium whereas broader isthmuses consist of thicker myocardium in corrected and uncorrected patients (Figure 3E-F).

DISCUSSION

To the best of our knowledge, this is the first and largest study of corrected and uncorrected post-mortem TOF specimens describing (i) isthmus presence and dimensions related to mode and timing of correction and (ii) in uncorrected specimens the age dependent dimensions of isthmus 3, i.e. the isthmus located between the PV and VSD-patch which is the result of the malformation itself. Based on our extensive collection of post-mortem TOF specimens, key findings are (1) that the routinely used transatrial-transpulmonary correction prevented the occurrence of isthmus 2 (isthmus between PV and non-transannular RV-incision/patch). Transventricular correction was in our collection after July 1975 only used in the presence of major coronary aberrancy. Second, mode of correction did not change the presence

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Table 5. Comparison of isthmus 3 between uncorrected and corrected patients.

	Uncorrected (n=58)	Corrected (n=84)	p
Age (years)	1.8 (0.5-6.6)	6.6 (4.0-11.5)	<0.001
Isthmus 3			
Present	55 (95%)	83 (99%)	0.159
Width (mm): all ages	9 (5-14)	8 (6-13)	0.943
Width (mm): <1y	5 (3-7)	6 (4-7)	0.649
Width (mm): 1 - <4y	11 (7-15)	7 (6-8)	0.028
Width (mm): 4 - <8y	13 (9-16)	8 (6-15)	0.391
Width (mm): 8 - <12y	15 (9-20)	10 (8-13)	0.038
Width (mm): 12 - <18y	8	15 (7-19)	0.410
Width (mm): >18y	23 (11-27)	10 (8-19)	0.330
Thickness (mm): all ages	4 (2-6)	5 (3-6)	0.721
Thickness (mm): <1y	2 (2-3)	4 (2-5)	0.279
Thickness (mm): 1 - <4y	6 (3-7)	4 (3-5)	0.068
Thickness (mm): 4 - <8y	6 (4-7)	5 (3-6)	0.247
Thickness (mm): 8 - <12y	8 (6-9)	5 (4-6)	0.020
Thickness (mm): 12 - <18y	4	6 (3-8)	0.513
Thickness (mm): >18y	7 (4-11)	6 (3-9)	0.604

Mm, millimeter; y, year.

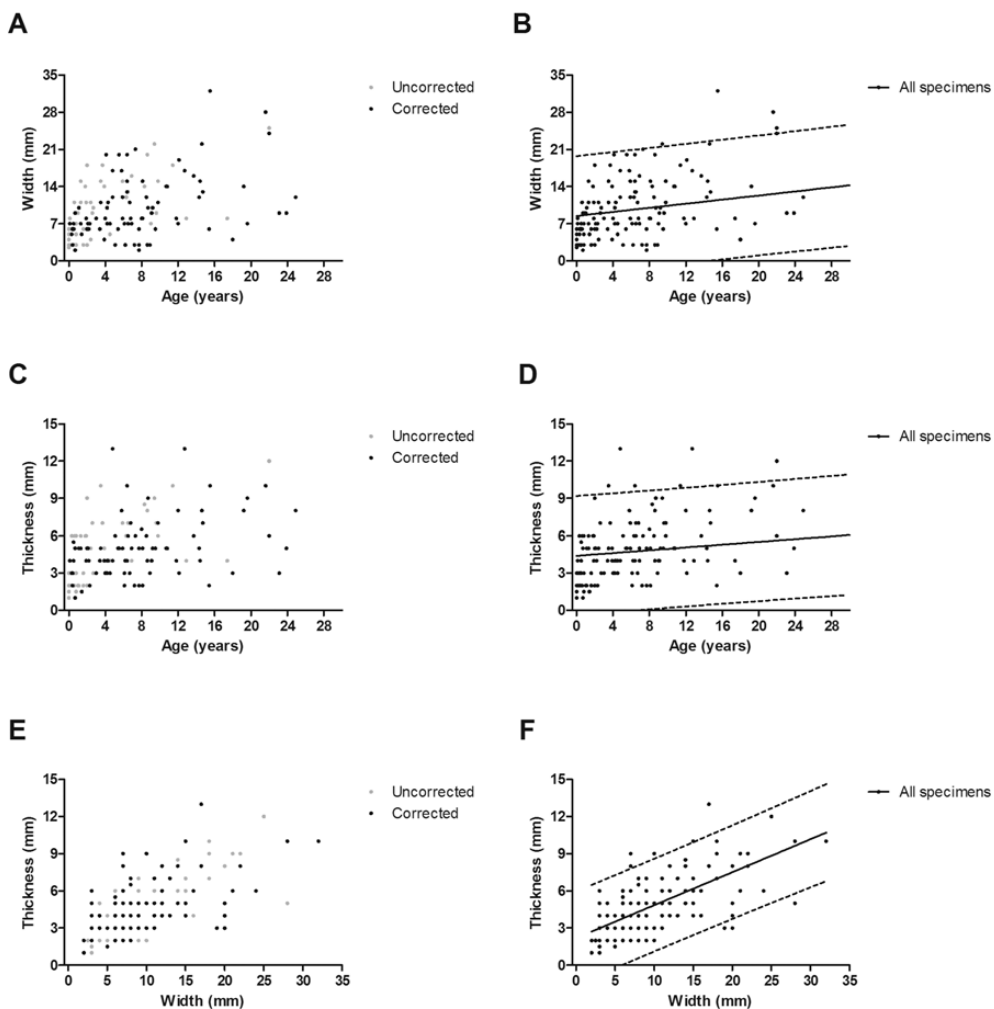


Figure 3. Scatterplots of isthmus 3 width and age (Panel A-B), scatterplots of isthmus 3 thickness and age (Panel C-D) and scatterplots of isthmus 3 thickness and width (Panel E-F). Panel A, C and E: uncorrected patients are marked with grey dots and corrected patients with black dots. Panel B, D and F: the mean and 95% confidence interval are marked.

and dimensions of isthmus 3. However, isthmus 1 (isthmus between tricuspid annulus and RVOT-patch/RV-incision) was thicker after the transatrial-transpulmonary correction. Third, a transatrial-transpulmonary correction <1 year as compared to >1 year resulted in the use of a smaller transannular patch, which may influence the dimensions of isthmus 1 over time. Fourth, the range of isthmus 3 dimensions was large among all ages in both uncorrected and corrected TOF specimens, with an association between isthmus width and thickness.

Influence of mode of repair

In our collection of post-mortem TOF specimens, the transatrial-transpulmonary correction prevented the occurrence of isthmus 2 and was routinely used after July 1975, whereas the transventricular approach was after July 1975 only used in case of coronary aberrancy (only 1 specimen). The prevalence of isthmus 1 and 3 (>both 90%) did not differ between both surgical approaches. The high prevalence of isthmus 1 and 3 is in line with recent large electroanatomical mapping studies^{6,7} and the anatomical study by Moore et al.¹² Of interest, after the transatrial-transpulmonary approach the myocardium of isthmus 1 remained thicker which may influence proarrhythmogenic remodeling over time. Of interest, isthmus 2, as compared to the other isthmuses, was relatively narrow and thin.¹² Electroanatomical studies have shown that anatomical isthmuses with slow conduction were significantly narrower as compared to anatomical isthmuses with normal conduction.⁷ A narrow and thin isthmus 1 and 2 may be more likely potentially arrhythmogenic. Accordingly, the transatrial-transpulmonary correction may reduce the risk of substrate formation by preventing isthmus 2 and by thicker isthmus 1.

Influence of timing in case of a transatrial-transpulmonary correction

In our cohort of specimens with transatrial-transpulmonary correction, there was no difference in presence and dimensions (if corrected for total RV length) of isthmus 1 and 3 between specimens corrected <1 year and ≥1 year. However, the transannular RVOT-patch, bordering isthmus 1, was 18 mm (95% CI: 6 – 30mm, $p=0.009$) smaller. Therefore, the smaller RVOT-patches in specimens with a transatrial-transpulmonary correction <1 year might eventually result in not only a thicker but also a broader isthmus 1 when the heart is fully grown as compared to specimens with a transatrial-transpulmonary correction ≥1 year. Recent mapping data demonstrated that anatomical isthmuses with normal conduction were indeed broader and had more preserved voltages suggesting thicker myocardium, as compared to those with slow conduction.⁷ Therefore, in specimens with a transatrial-transpulmonary and with a correction <1 year, isthmus 1 may have less often the arrhythmogenic isthmus characteristics (narrow, thin) that are typical for VT related isthmuses.

Isthmus 3 is, as compared to isthmus 1, more narrow and thinner¹² and therefore potentially more often slow conducting and related to VT, which has been confirmed by two large mapping studies.^{6,7} Despite early repair, isthmus 3 may be arrhythmogenic, as demonstrated in a cohort of 15 cTOF patients corrected <2 years in which 5 patients (33%) had a slow conducting isthmus which was proven related to VT in 4.⁷ Therefore, we consider isthmus 3 to be the most important potentially arrhythmogenic isthmus in the present surgical era in which most patients undergo a transatrial-transpulmonary correction <1 year.

Isthmus 3: uncorrected versus corrected

In our population of post-mortem TOF specimens the range of isthmus 3 dimensions (width and thickness, Figure 3) was wide across all ages in both uncorrected and corrected

TOF specimens which might be a reflection of the broad anatomical spectrum of the malformation. Of importance, there was a strong correlation between width and thickness of isthmus 3 in uncorrected and corrected specimen implying that a narrow isthmus consists of thinner myocardium. Considering the association between isthmus width and slow conduction found in clinical mapping studies we may speculate that in particular a narrow isthmus 3, which width is not influenced by the initial repair may show pathological remodeling over time providing the substrate for slow conduction and VT.

It has been shown that the RVOT contains interstitial and replacement fibrosis and that the amount of fibrosis is associated with the duration of pressure overload (i.e. age of repair).¹³ Myocyte bundles separated and interspersed by fibrosis provide the substrate for reentry VTs. We hypothesize that slow conduction might evolve over time, which may be due to adverse remodeling at the border zone between patch material and/or dense fibrosis, similar what has been observed at the border zone of myocardial infarction. Adverse remodeling may further be promoted by late volume overload in patients with pulmonary valve regurgitation. Further studies are required to gain more insight in the substrate for slow conduction of isthmus 3 despite early repair.

Clinical implications

The current routine use of transatrial-transpulmonary correction <1 year as compared to the previous mode and timing of correction prevented isthmus 2, resulted in a thicker isthmus 1 and may result in a broader isthmus 1 in the adult heart, if a smaller transannular RVOT-patch has been used. As VT related anatomical isthmuses in the adult TOF are typically narrow with low voltages consistent with a thin layer of viable myocardium⁷, the thicker and broader isthmus 1 may less likely serve as a substrate for late VT. Accordingly, the modern surgical approach is likely to reduce the risk for VT. In the present surgical era, isthmus 3, however, may remain as the only potential proarrhythmogenic isthmus. As demonstrated this isthmus is not dependent on the type and timing of surgery but on the variation of the malformation. We may therefore consider a preventive intraoperative ablation of a 'narrow and thin' isthmus 3 during initial repair and, as standard procedure, if re-operation needs to be performed. In patients who do not need re-operation, but who are considered at risk for VT may undergo invasive VT risk stratification by electroanatomical mapping and, if inducible, subsequent ablation.⁷ Isthmuses 3 that are related to VT as compared to isthmuses 3 that are not related to VT tended to be narrower and had lower voltages consistent with a thin layer of viable myocardium and subsequently required only short ablation lines in prior clinical investigations.⁷ Therefore, radiofrequency catheter ablation of isthmus 3 related VT could be performed with a high acute success rate, and with freedom of VT during long-term follow-up.⁶ Identification of narrow and slow-conducting AI currently requires invasive electroanatomical mapping.⁷ To overcome the need for invasive VT risk stratification in TOF, it would be interesting to further explore if contrast enhanced cardiac magnetic resonance imaging (CE-MRI) can reliably delineate anatomical isthmuses. Of

importance, there is currently no cutoff value for isthmus size with sufficient discriminative power for individualized VT risk stratification.⁷ In contrast, an isthmus conduction velocity of $<0.5\text{m/s}$ has been shown to have sufficient discriminative power for individualized VT risk stratification. Therefore, additional CE-MRI derived imaging criteria need to be evaluated that might be able to identify tissue characteristics consistent with slow conduction.

Limitations

Most corrected patients died shortly after correction at an age of <18 years. Therefore, the study cohort is not fully representative for the population of adult TOF patients (with VT). There was too little clinical data on the occurrence of VT to perform analyses between isthmus characteristics and VT. Nevertheless, this study comprises the largest cohort of post-mortem TOF specimens over a long time span ranging from a period of 1936 to 2007, and the first to demonstrate a relation between on one hand isthmus presence and dimensions and the other hand mode and timing of correction which is relevant for VT risk of present and future TOF patients.

CONCLUSION

The current routine use of transatrial-transpulmonary correction as compared to the only incidental use of the ventricular correction prevented the presence of isthmus 2 and was associated with thicker isthmus 1. Transatrial-transpulmonary correction <1 year as compared to ≥ 1 year resulted in a smaller transannular patch, which might result in a broader isthmus 1 when the heart is fully grown. Mode and timing of correction did not change prevalence and dimensions of isthmus 3. In uncorrected and corrected post-mortem TOF specimens, the range of isthmus 3 dimensions was broad across all ages. The strong association between isthmus 3 width and thickness and the clinical association between a narrow isthmus and slow conduction facilitating VT may have important implication for the management of contemporary TOF patients. A narrow isthmus 3 may remain the only potential substrate for late VTs which could be targeted during initial repair or re-operation.

ACKNOWLEDGMENTS

We are grateful to thank R. Slagter for drawing the schematic hearts in figure 1.

KEY QUESTIONS

What is already known about this subject?

Ventricular tachycardia (VT) is an important cause for late mortality and morbidity in corrected tetralogy of Fallot (TOF). The dominant substrate for VT in TOF are anatomical isthmuses with slow conduction. There are four anatomical isthmuses which are the result of the malformation itself and surgical correction.

What does this study add?

This study supports the hypothesis that the current routine use of transatrial-transpulmonary correction below the age of 1 year prevents isthmus 2 (between pulmonary valve (PV) and right ventricular (RV) incision/RV outflow tract (RVOT) patch) and is associated with thicker myocardium within isthmus 1 (between tricuspid annulus and RV-incision/RVOT-patch). In addition, the reduced transannular-patch size may result in a broader isthmus 1 later in life. Mode and timing of repair did not influence dimensions of isthmus 3 (between PV and ventricular septal defect patch) which varied widely across all ages. The demonstrated association between isthmus 3 width and thickness of the myocardium and the earlier demonstrated clinical association between narrow isthmus 3 and VT strongly suggest that a narrow isthmus 3 is likely to undergo pro-arrhythmogenic remodeling over time.

How might this impact on clinical practice?

In TOF, isthmus 3, especially a narrow isthmus 3, may be the last remaining potentially arrhythmogenic isthmus and may be a target for preventive ablation during initial repair or re-operation.

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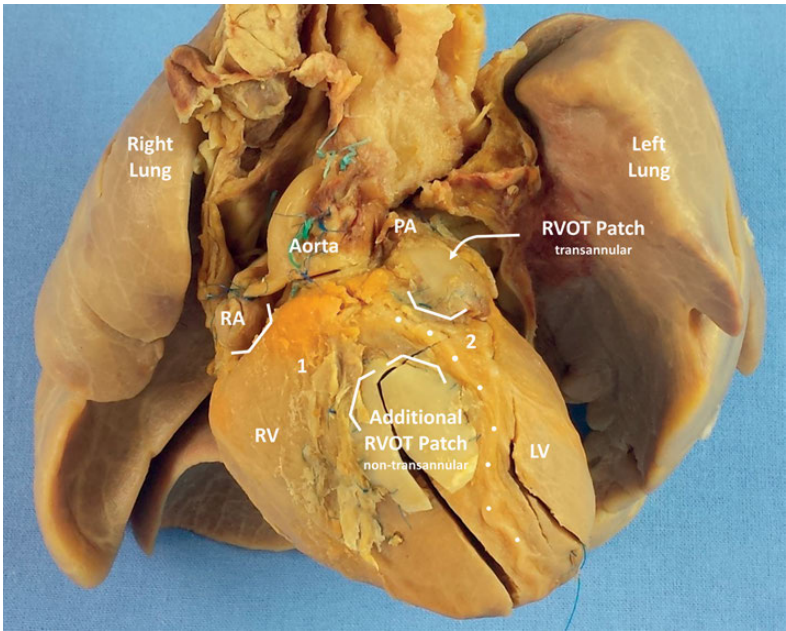
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SUPPLEMENT A

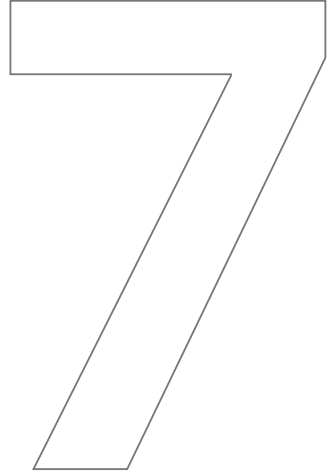
A1. Table, additional baseline characteristics, previous palliative operations.

	All corrected patients (n=84)	Transventricular correction (n=35)	Transatrial-transpulmonary correction (n=49)	p
Palliative operation before correction	39 (46%)	18 (51%)	21 (43%)	0.437
Age (y)	3.0 (1.4-4.9)	2.9 (1.6-5.0)	3.5 (0.6-4.9)	0.988
Interval first PO - correction (y)	4.2 (2.2-8.5)	4.6 (2.9-9.9)	4.0 (2.0-6.0)	0.313
Type				
Brock	1 (3%)	1 (6%)	0 (0%)	0.102
Shunt - Potts	11 (28%)	8 (44%)	3 (14%)	
Shunt - Waterston	4 (10%)	1 (6%)	3 (14%)	
Shunt - Blalock Taussig	23 (59%)	8 (44%)	15 (71%)	

PO, palliative operation; y, year.



A2. TOF patient with LAD from RCA crossing over right ventricular outflow tract, subsequently corrected with transventricular approach. TOF patient corrected with transventricular approach after July 1975. Isthmus 2 (marked with brackets) located between two right ventricular outflow tract (RVOT) patches due to an aberrant left anterior descending artery (LAD). The aberrant LAD (marked with •) originates from the right coronary artery. Isthmus 1 is also present, located between the non-transannular RVOT patch and the tricuspid annulus. LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.



Summary, Conclusions and Future Perspectives

SUMMARY

This thesis describes the anatomical features, repair and epidemiology of tetralogy of Fallot (TOF) and the challenges of non-invasive risk stratification and invasive treatment of ventricular tachycardia in TOF. TOF is classically characterized by a (sub)pulmonary stenosis, ventricular septal defect (VSD), overriding of the aortic orifice and secondary concentric right ventricular (RV) hypertrophy. During repair, the VSD is closed with a patch and the (sub)pulmonary stenosis is relieved. In the past, repair was performed via a transventricular approach in the first decade of life. Nowadays, repair is performed via a transatrial-transpulmonary approach in the first year of life. Due to the good surgical outcome, the prevalence of adults with TOF has doubled between 1980 and 2010 from 0.1 to 0.2 per 1000 adults and is expected to increase even further. Adults with TOF still have a 29 fold higher risk to die suddenly as compared to healthy matched controls. The burden of ventricular arrhythmias in TOF is considerable with a prevalence of 15%, observed in a cohort of 556 adult TOF patients with a mean age of 37 ± 12 years. Eighty percent of these ventricular arrhythmias are fast monomorphic macro-reentrant ventricular tachycardia (average of 213 beats per minute) and related to anatomical isthmuses. The anatomical isthmuses in TOF are the result of the malformation itself or the surgical repair and are bordered by valve annuli, patch-material and/or incisions. The value of non-invasive risk factors is limited. A limited number of case series and very small cohorts studies reported that radiofrequency catheter ablation of VT in adults with TOF is a feasible option, especially substrate mapping permits ablation of fast and hemodynamically unstable VTs.

In **chapter two**, in a cohort of 74 repaired TOF patients who were considered at risk for VT, the properties of the anatomical isthmuses (i.e. width, length and conduction velocity) were determined by electroanatomical mapping during sinus rhythm. All patients had a least one anatomical isthmus and 28 patients were inducible for 41 VTs. The anatomical isthmuses of the 28 patients with inducible VT as compared to anatomical isthmuses of the 46 patients without inducible VT were narrower and longer and demonstrated a lower conduction velocity index (CVi). Thirty-seven of the 41 inducible VTs were mapped to an anatomical isthmus. All anatomical isthmuses related to VT had a conduction velocity of $<0.5\text{m/s}$ (defined as slow conducting anatomical isthmus). In contrast, 87 of 89 anatomical isthmuses in 46 patients without inducible VT had a CVi of $\geq 0.5\text{m/s}$. All 62 patients without a slow conducting anatomical isthmus, 44 at baseline and 18 after ablation, were free from VT during a follow-up of 262 patient years (average 5 ± 2 years). The reported ventricular arrhythmia event rates in patients with comparable risks factors who received an ICD for primary or secondary prevention were 8-10% per year, which was also observed in our cohort of patients discharged with a slow conducting anatomical isthmus. These findings confirm the strong link between slow conducting anatomical isthmuses and VT in TOF.

Chapter three describes the acute and long-term outcome of radiofrequency catheter ablation (RFCA) of anatomical isthmus related VT with the use of substrate mapping in a large group of 34 patients with repaired congenital heart disease. Twenty-eight of 34 patients had

TOF. These 34 patients were inducible for a median of 1 (inter quartile range: 1 – 2) VT and VTs were fast with a median cycle length of 295ms (inter quartile range: 242 – 346). Acute success, defined as bidirectional block of the anatomical isthmus that contained the critical VT re-entry site and non-inducibility of any VT after ablation, was achieved in 25 patients (74%). All 25 patients with acute success remained free from VT during follow-up (4 ± 2 years), only 1 patient with a depressed cardiac function and an ICD experienced an episode of ventricular fibrillation. In contrast, 4 of the 9 patients without acute success experienced VT during long-term follow-up.

In the cohort, described in Chapter 3, of the 28 consecutive TOF patients that underwent radiofrequency catheter ablation of anatomical isthmus related VT, VT ablation failed in 11 patients after a right-sided procedure. VT was mapped in 8 of these 11 patients to a septal anatomical isthmus. A left-sided approach was not performed in 4 patients due to procedural reasons such as procedure length, patient condition and/or pathology of the aortic valve. The 4 patients that did undergo a left-sided approach are reported in **chapter four**. In 3 patients with a left-sided approach, radiofrequency catheter ablation in the aortic root resulted in acute success. In 1 patient with prior biventricular cardioverter-defibrillator implantation diastolic activity during VT was recorded at the His-bundle and ablation resulted in acute success and as anticipated in AV-block. The right-sided failure in these four patients was probably due to hypertrophy of the myocardium, an overlying pulmonary homograft and VSD-patch. All four patients remained free from VT during a follow-up of 2 ± 1 years.

The **fifth chapter** describes the contribution of the VT substrate to QRS duration according to absence or presence of right bundle branch block (RBBB) in a cohort 78 TOF patients that underwent VT induction and electroanatomical mapping during sinus rhythm. Twenty-four patients were inducible for VT, 22 of the 24 patients with VT had a slow conducting anatomical isthmus. In contrast, only 2 of the 54 patients without VT had a slow conducting anatomical isthmus. As expected the conduction velocity through the anatomical isthmuses was lower in patients with VT. There was no difference in remote RV conduction velocity and RV size between patients with and without VT. In the 11 patients with a narrow QRS, the QRS duration was similar for patients with and without VT. However, total RV activation time and RV activation after QRS-offset were significantly longer in narrow QRS patients with VT. The RV activation after QRS-offset was confined to the slow conducting anatomical isthmuses not contributing to the 12 lead ECG. In the 67 RBBB patients, both total RV activation time and QRS duration were longer in patients with inducible VT. RBBB patients with QRS duration ≥ 150 ms as compared to RBBB patients with QRS duration < 150 ms were 14 times more like to be inducible for VT.

The **final chapter (Chapter 6)** reports on the influence of repair itself, mode of repair and timing of repair on anatomical isthmus presence and dimensions in a cohort of 142 TOF post-mortem specimens (84 corrected and 58 uncorrected). Anatomical isthmus 1, the isthmus between the tricuspid annulus and RVOT-patch/RV-incision, and isthmus 3, isthmus between the pulmonary annulus and VSD, were the most prevalent anatomical isthmuses and present

in 99% of the specimens. The currently used transatrial-transpulmonary repair as compared to transventricular repair prevented isthmus 2, the isthmus between pulmonary annulus and RVOT-patch/RV-incision, and was associated with a thicker isthmus 1. Transatrial-transpulmonary correction <1 year as compared to ≥ 1 year resulted in a smaller transannular patch, which might result in a broader isthmus 1 when the heart is fully grown. Mode and timing of correction did not change prevalence and dimensions of isthmus 3. In uncorrected and corrected post-mortem TOF specimens, the range of isthmus 3 dimensions was broad across all ages. The strong association between isthmus 3 width and thickness and the clinical association between a narrow isthmus and slow conduction facilitating VT may have important implication for the management of contemporary TOF patients. A narrow isthmus 3 may remain the only potential substrate for late VTs in the present surgical era.

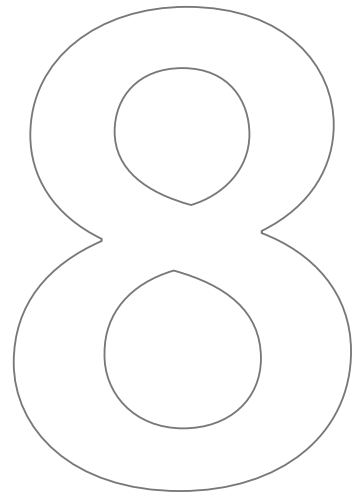
CONCLUSIONS

The prevalence of adults with TOF is 0.2 per 1000 adults and is expected to further increase due to the good surgical outcome. Nevertheless, adults with TOF still have a 29 fold higher risk to die suddenly as compared to healthy matched controls. The burden of ventricular arrhythmias in TOF is considerable with a prevalence of 15% and are an important cause for late morbidity and mortality. The majority of the ventricular arrhythmias are monomorphic VT. The dominant substrate for VT in TOF are slow conducting anatomical isthmuses which can be identified by electroanatomical mapping during sinus rhythm allowing individualized risk stratification and preventive ablation. Radiofrequency catheter ablation of anatomical isthmus related VT in repaired congenital heart disease, especially in TOF, can be performed with a high acute success rate. In case of right-sided failure of radiofrequency catheter ablation of septal anatomical isthmus related VT in TOF, left-sided ablation can be performed successfully and safely. Provided that bidirectional block of the anatomical isthmus that contains the critical VT re-entry site is achieved, radiofrequency catheter ablation of anatomical isthmus related VT in TOF can be even considered curative and prevent ICD implantation in presence of a preserved cardiac function. Slow conducting anatomical isthmuses are an important link between QRS duration and risk of VT in TOF patients. In TOF patients with pre-existing right bundle branch block, the slow conducting anatomical isthmuses prolong right ventricular activation time and QRS duration. A narrow QRS in TOF does not exclude VT and presence of a slow conducting anatomical isthmus. In TOF, the most prevalent arrhythmogenic anatomical isthmus is the isthmus between the pulmonary valve and ventricular septal defect, i.e. isthmus 3. Isthmus 3 is not influenced by repair itself, nor by mode or timing of repair. Therefore isthmus 3 is expected to remain the most important arrhythmogenic isthmus in future TOF patients.

FUTURE PERSPECTIVES

The dominant substrate for VT in TOF are slow conducting anatomical isthmuses which can be identified by electroanatomical mapping during sinus rhythm allowing individualized

risk stratification and preventive ablation, which can be curative and can in presence of a preserved biventricular function prevent ICD implantation. Currently we do not know the best moment for invasive risk stratification and we do not know if one procedure is sufficient. Further studies focusing on the mechanism of slow conduction within these anatomical isthmuses of TOF patients is required in order to optimally time invasive VT risk stratification and/or preventive VT ablation possibly during re-operation or even during initial repair.



Samenvatting, Conclusies en Toekomstperspectief

Publications

Dankwoord

Curriculum Vitae

SAMENVATTING

In dit proefschrift worden de anatomische kenmerken, correctie en epidemiologie van tetralogie van Fallot (TOF) en de uitdagingen van niet-invasieve risico stratificatie en invasieve behandeling van ventrikel tachycardie (VT) in TOF beschreven. Klassieke TOF wordt gekenmerkt door een (sub)pulmonale stenose, ventrikel septum defect (VSD), overrijdende aorta en hieraan secundaire concentrische rechter ventrikel (RV) hypertrofie. De chirurgische correctie bestaat uit het sluiten van het VSD met een patch en het opheffen van de (sub) pulmonale stenose. In het verleden werd de correctie verricht middels een transventriculaire benadering binnen de eerste 10 jaar van het leven. De transventriculaire benadering houdt in dat de chirurgische correctie wordt uitgevoerd via een incisie in de RV. Tegenwoordig wordt de correctie verricht via een transatriale-transpulmonale benadering in het eerste levensjaar. De transatriale-transpulmonale benadering houdt in dat de chirurgische correctie wordt uitgevoerd via een incisie in het rechter atrium en de arteria pulmonalis. De goede chirurgische technieken hebben geresulteerd in een verbetering van de overleving, met verdubbeling van de prevalentie van volwassenen met TOF tussen 1980 en 2010, namelijk van 0.1 naar 0.2 per 1000 volwassenen. Er wordt verwacht dat de prevalentie van volwassen met TOF nog zelfs verder zal toenemen. Volwassenen met TOF hebben een 29 maal zo hoog risico om plots te overlijden ten op zichten van gezonde leeftijdsgenoten. De prevalentie van ventriculaire ritmestoornissen in TOF is met 15% behoorlijk hoog. Deze hoge prevalentie werd geobserveerd in een cohort van 556 volwassen TOF patiënten met een gemiddelde leeftijd van 37 ± 12 jaar. Tachtig procent van deze ventriculaire ritmestoornissen zijn snelle monomorfe macro reentry ventrikel tachycardieën met een gemiddelde snelheid van 213 slagen per minuut en gerelateerd aan anatomische isthmuses. Een anatomische isthmus is een smal stukje hartspierweefsel dat aan beide kanten wordt begrensd door anatomische structuren. De anatomische isthmuses in TOF zijn inherent aan het congenitale defect of het gevolg van de chirurgische correctie en worden begrensd door klepringen, patch materiaal en/of RV incisies. Het voorspellend vermogen van niet-invasieve risicofactoren voor VT is beperkt. Een beperkt aantal cases en zeer kleine cohort studies hebben aangetoond dat radiofrequente katheter ablatie van VT in volwassenen met TOF een aantrekkelijk optie is, waarbij substraat mapping het mogelijk maakt om snelle en hemodynamische instabiele VT te ableren. Ableren houdt in dat een klein stukje hartspierweefsel wordt opgewarmd of wordt bevroren waardoor littekenweefsel ontstaat. Het geableerde hartspierweefsel kan vervolgens geen elektriciteit meer geleiden. In het geval van het ableren van een VT wordt het kritieke onderdeel van het VT circuit geableerd waardoor het VT circuit wordt onderbroken.

In hoofdstuk twee werden de eigenschappen van de anatomische isthmus (breedte, lengte en geleidingssnelheid) gemeten in 74 gecorrigeerde TOF patiënten, die risico lopen op VT, met het gebruik van elektro anatomische mapping tijdens sinus ritme. Elektro anatomische mapping houdt in dat de elektrische activatie op meerdere plekken in het hart wordt gemeten waarvan vervolgens een kaart, een map, wordt gemaakt. Een elektro

anatomische map geeft vervolgens een duidelijk overzicht van de elektrische activatie van het hart. Alle TOF patiënten hadden tenminste 1 anatomische isthmus en 28 patiënten waren induceerbaar voor 41 VT. De anatomische isthmus van de 28 patiënten met VT ten op zichten van de 46 patiënten zonder VT waren smaller, langer en hadden een lagere geleidingssnelheid. Zevenendertig van de 41 VT waren gerelateerd aan een anatomische isthmus. Alle VT gerelateerde anatomische isthmuses hadden een geleidingssnelheid van <0.5 m/s (gedefinieerd als een traag geleidende anatomische isthmus). Daarentegen, 87 van 89 anatomische isthmuses van de 46 patiënten zonder VT hadden een geleidingssnelheid van ≥ 0.5 m/s. Alle 62 patiënten zonder traag geleide anatomische isthmus, 44 patiënten bij de eerste beoordeling en 18 patiënten na ablatie, hadden geen VT tijdens een periode van 262 patiëntjaren (gemiddeld 5 ± 2 jaar per patiënt). Eerdere studies in patiënten met vergelijkbare risicofactoren en een ICD (primaire en secundaire preventie) hebben een VT prevalentie van 8-10% per jaar aangetoond. Deze prevalentie was gelijk in ons cohort van TOF patiënten die ontslagen werden met een traag geleidende anatomische isthmus. Dit bevestigt de sterke associatie tussen traag geleidende anatomische isthmus en VT in TOF.

Hoofdstuk 3 beschrijft de directe en lange termijn uitkomst van radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT met behulp van substraat mapping in een grote groep van 34 patiënten met een gecorrigeerde aangeboren hart afwijking. Achtentwintig van de 34 patiënten hadden TOF. Deze 34 patiënten waren induceerbaar voor snelle VT met een mediane cyclus lengte van 295ms (inter kwartiel: 242 – 346). Acuut succes, gedefinieerd als bidirectionele blokkade van de anatomische isthmus die gerelateerd was aan de VT en niet-induceerbaarheid van VT na ablatie, werd behaald in 25 patiënten (74%). Alle 25 patiënten met acuut succes hadden geen VT tijdens follow-up (4 ± 2 jaar), slechts 1 patiënt met hartfalen kreeg een ICD schok voor ventrikel fibrilleren. Daarentegen hadden 4 van 9 patiënten zonder acuut succes een VT recidief.

In het cohort van de 28 TOF patiënten, die radiofrequente katheter ablatie van anatomische isthmus gerelateerde VT ondergingen (Hoofdstuk 3), was VT ablatie in 11 patiënten niet succesvol na een rechtszijdige benadering. De VT was in 8 van de 11 patiënten gerelateerd aan een septale anatomische isthmus. Een septale anatomische isthmus is gelegen tussen beide ventrikels. Een linkszijdige benadering werd niet verricht in 4 patiënten vanwege procedure tijd, conditie van de patiënt en/of aortaklep pathologie. De overige 4 patiënten die wel een linkszijdige procedure ondergingen werden beschreven in hoofdstuk 4. Radiofrequente katheter ablatie in de aortawortel termineerde VT en resulteerde in acuut succes in 3 patiënten. In 1 patiënt met reeds een biventriculaire ICD werd diastolische activiteit gezien ter plaatse van de His-bundel waar ablatie resulteerde in acuut succes en zoals verwacht in totaal AV-blok. Rechtszijdige ablatie lukte in deze patiënten waarschijnlijk niet vanwege hypertrofie van het myocard, een overliggende pulmonalis homograft of VSD-patch. Alle vier patiënten met een linkszijdige procedure hadden geen VT tijdens follow-up (2 ± 1 jaar).

Het vijfde hoofdstuk beschrijft de bijdrage van het VT substraat aan QRS duur in de afwezigheid en aanwezigheid van een rechter bundeltak blok (RBTB) in een cohort

van 78 TOF patiënten die VT inductie en elektro anatomische mapping tijdens sinus ritme ondergingen. Vierentwintig patiënten waren induceerbaar voor VT, 22 van de 24 patiënten met VT hadden een traag geleidende anatomische isthmus. Een traag geleidende anatomische isthmus werd in slechts 2 van de 54 patiënten zonder VT geobserveerd. De geleidingssnelheid van de anatomische isthmus van patiënten met VT was, zoals verwacht, lager. Er was geen verschil in RV geleidingssnelheid en RV grootte tussen patiënten met en zonder VT. In de 11 patiënten met een smal QRS complex was er geen verschil in QRS duur tussen patiënten met en zonder VT. Echter, de totale RV activatie tijd en de RV activatie na het einde van het QRS complex waren beide langer in patiënten met een smal QRS complex en VT. De RV activatie na het einde van het QRS complex was gelokaliseerd ter plaatse van de traag geleidende anatomische isthmus, derhalve droeg deze niet bij aan het oppervlakte ECG. In de 67 patiënten met RBTB waren zowel de totale RV activatie tijd als de QRS duur langer in RBTB patiënten met VT ten opzichte van RBTB patiënten zonder VT. RBTB patiënten met een QRS duur ≥ 150 ms ten opzichte van <150 ms hadden een 14 maal zo hoge kans op induceerbare VT.

Het laatste hoofdstuk (Hoofdstuk 6) beschrijft de invloed van de correctie zelf, methode van de correctie en moment van de correctie op de aanwezigheid en eigenschappen van de anatomische isthmus in een cohort van 142 post mortem TOF harten (84 gecorrigeerd, 58 ongecorrigeerd). Anatomische isthmus 1, de isthmus tussen de tricuspidalis annulus en een RVOT patch/RV incisie, en anatomische isthmus 3, de isthmus tussen de pulmonalis annulus en het VSD, waren de meest prevalentie anatomische isthmus en aanwezig in 99% van de post mortem TOF harten. De huidige transatriale-transpulmonale methode ten opzichte van de transventriculaire methode zorgde ervoor dat anatomische isthmus 2, de isthmus tussen de pulmonalis annulus en een RVOT patch/RV incisie, niet meer aanwezig was en was geassocieerd met een dikkere isthmus 1. De transatriale-transpulmonale methode onder de leeftijd van 1 jaar ten opzichte van ≥ 1 jaar resulteerde in het gebruik van een kleinere RVOT-patch, die uiteindelijk zou kunnen resulteren in een bredere isthmus 1 op het moment dat het hart volgroeid is. De methode en het moment van correctie hadden geen invloed op de aanwezigheid en dimensies van isthmus 3. De spreiding van isthmus 3 dimensies (dikte en breedte) was groot op alle leeftijden in zowel gecorrigeerde als ongecorrigeerde post mortem TOF harten. De sterke associatie tussen de breedte en dikte van isthmus 3 en de bekende klinische associatie tussen een smalle anatomische isthmus en trage geleiding welke VT faciliteren, hebben belangrijke implicaties voor behandeling van huidige TOF patiënten. Een smalle isthmus 3 is mogelijk nog het enige substraat voor VT in TOF in het huidige chirurgische tijdsvlak.

CONCLUSIES

De prevalentie van volwassenen met TOF is 0.2 per 1000 volwassenen en zal verder toenemen vanwege de goede chirurgische resultaten. Volwassenen met TOF hebben desalniettemin een 29 maal hoger risico om plotseling te overlijden ten opzichte van

gezonde leeftijdsgenoten. De prevalentie van ventriculaire ritmestoornissen in volwassen TOF patiënten is hoog met 15%. Ventriculaire ritmestoornissen in TOF zijn een belangrijke oorzaak voor morbiditeit en mortaliteit bij volwassenen. Het merendeel van deze ventriculaire ritmestoornissen zijn monomorfe VTs. Het dominante substraat voor VT in TOF zijn traag geleidende anatomische isthmuses die geïdentificeerd kunnen worden met elektro anatomische mapping tijdens sinus ritme waardoor individuele risicostratificatie en preventieve ablatie mogelijk is. Radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT in corrigeerde aangeboren hartafwijkingen kan worden uitgevoerd met een hoog acuut succes, met name in TOF. In het geval dat rechtszijdige radiofrequente katheter ablatie van een septale anatomisch isthmus gerelateerde VT in TOF niet succesvol is, kan linkszijdige ablatie veilig en succesvol worden verricht. Op het moment dat bidirectioneel blok bereikt kan worden van de anatomische isthmus die de kritieke isthmus van de VT bevat, kan radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT als curatief worden beschouwd en kan zelfs in patiënten met een behouden hartfunctie een ICD implantatie voorkomen. De traag geleidende anatomische isthmuses zijn een belangrijke link tussen de QRS duur en het risico op VT in TOF patiënten. De traag geleidende anatomische isthmus in TOF patiënten met RBTB verlengen namelijk de totale RV activatie tijd en QRS duur. Een smal QRS complex in TOF sluit echter VT en de aanwezigheid van een traag geleidende anatomische isthmus niet uit. De meest prevalentie aritmogene isthmus in TOF is de isthmus tussen de pulmonalis annulus en het VSD, namelijk isthmus 3. Isthmus 3 wordt niet beïnvloed door de correctie zelf, niet door methode van correctie en niet door het moment van correctie. Het is daarom de verwachting dat anatomische isthmus 3 de meest aritmogene anatomische isthmus zal blijven in toekomstige TOF patiënten.

TOEKOMSPERSPECTIEF

Het dominante substraat voor VT in TOF zijn traag geleidende anatomische isthmuses die geïdentificeerd kunnen worden met elektro anatomische mapping tijdens sinus ritme waardoor individuele risicostratificatie en preventieve ablatie mogelijk is. Een succesvolle radiofrequente katheter ablatie van anatomisch isthmus gerelateerde VT in TOF kan als curatief worden beschouwd en kan bij behouden hartfunctie zelfs ICD implantatie voorkomen. Op dit moment is het onbekend wat het beste moment is voor invasieve risicostratificatie en het is onbekend of één procedure voldoende is. Toekomstige studies zouden daarom gericht moeten worden op het ophelderen van het mechanisme achter het ontstaan van trage geleiding van de anatomische isthmus in TOF om op die manier het beste moment vast te stellen voor invasieve risicostratificatie en/of preventieve ablatie mogelijk tijdens her-operatie of zelfs tijdens de initiële correctie.

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DANKWOORD

Dit proefschrift is tot stand gekomen op de afdeling Hartziekten van het Leids Universitair Medisch Centrum. Mijn dank gaat uit naar iedereen die een bijdrage heeft geleverd aan dit proefschrift. In de eerste plaats naar de patiënten op wiens gegevens dit proefschrift is gebaseerd.

Mijn promotor wil ik bedanken voor de begeleiding bij dit proefschrift. Beste prof. Zeppenfeld, beste Katja, de samenwerking met jou was zeer inspirerend waarbij het streven naar perfectie en de internationale samenwerking elk project uniek maakte.

Mijn copromotor wil ik ook bedanken voor de begeleiding. Beste dr. Jongbloed, beste Monique, mijn dank gaat tevens uit naar het bevlogen anatomie onderwijs van jou en Margot, jullie flexibele agenda en gezellige tijd op de afdeling Anatomie en Embryologie.

Bij deze wil ik in het bijzonder dr. Verhorst bedanken voor de gegeven tijd, ruimte en interesse in mijn promotie, daarnaast wil ik dr. Verhorst en prof. Bax bedanken voor het gestelde vertrouwen.

Dear prof. Stevenson and dr. Reichlin from the Brigham and Women's Hospital, I would like thank you for the nice and productive collaboration. Dear dr. Reichlin, dear Tobias, I enjoyed our discussions at the congresses very much. Dear dr. Sacher and dr. Jalal from Bordeaux University Hospital, I would also like to thank you for the nice and productive collaboration.

Mijn opleider van de interne geneeskunde, dr. Anten uit het Alrijne Ziekenhuis Leiderdorp, wil ik ook bedanken. Beste Sander, bedankt voor de tijd, ruimte en interesse in mijn promotie.

Lieve moeder en Maaïke, bedankt voor jullie ondersteuning en ontspanning tijdens het schrijven van dit proefschrift.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 24 oktober 1986 in Leiderdorp. In 2005 behaalde hij zijn eindexamen Gymnasium cum laude aan het Bonaventura College te Leiden. Van 2005 tot en met 2012 studeerde hij geneeskunde aan Universiteit Leiden. Hij was tijdens zijn studie geneeskunde werkzaam als Joshua (IC-ondersteuner) op de thorax intensive care in het Leids Universitair Medisch Centrum. Hij was tevens betrokken bij wetenschappelijk onderzoek naar pulmonale hypertensie bij dr. H. Vliegen en dr. R.W.C. Scherptong. Na het cum laude behalen van zijn artsexamen in 2012, begon hij direct met een promotie traject onder leiding van prof. K. Zeppenfeld op de afdeling cardiologie in het Leids Universitair Medisch Centrum. De resultaten van dit promotie traject worden beschreven in dit proefschrift. Per 1 december 2014 is hij begonnen met de opleiding cardiologie aan Medisch Spectrum Twente (opleider: dr. P. Verhorst). Hij startte in januari 2016 met de vooropleiding Interne Geneeskunde in het Alrijne Ziekenhuis (opleider: dr. S. Anten) welke eind 2017 werd afgerond. De opleiding cardiologie werd daarna in 2018 voortgezet in Medisch Spectrum Twente.

