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Right atrial area and right ventricular outflow tract akinetic length predict sustained tachyarrhythmia in repaired tetralogy of Fallot

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ABSTRACT

Aims: Repaired tetralogy of Fallot (rtoF) patients are at risk of atrial or ventricular tachyarrhythmia and sudden cardiac death. Risk stratification for arrhythmia remains difficult.
We investigated whether cardiac anatomy and function predict arrhythmia.
Methods: One-hundred-and-fifty-four adults with rtoF, median age 30.8 (21.9–40.2) years, were studied with a standardised protocol including cardiovascular magnetic resonance (CMR) and prospectively followed up over median 5.6 (4.6–7.0) years for the pre-specified endpoints of new-onset atrial or ventricular tachyarrhythmia (sustained ventricular tachycardia/ventricular fibrillation).
Results: Atrial tachyarrhythmia (n = 11) was predicted by maximal right atrial area indexed to body surface area (RAAi) on four-chamber cine-CMR (Hazard ratio 1.17, 95% Confidence Interval 1.07–1.28 per cm^2/m^2; p = 0.0005, survival receiver operating curve; ROC analysis, area under curve; AUC 0.74 [0.66–0.81]; cut-off value 16 cm^2/m^2). Atrial arrhythmia-free survival was reduced in patients with RAAi ≥16 cm^2/m^2 (logrank p = 0.0001). Right ventricular (RV) restrictive physiology on echocardiography (n = 38) related to higher RAAi (p = 0.02) and had similar RV dilatation compared with remaining patients.
Ventricular arrhythmia (n = 9) was predicted by CMR RV outflow tract (RVOT) akinetic area length (Hazard ratio 1.05, 95% Confidence Interval 1.01–1.09 per mm; p = 0.003, survival ROC analysis, AUC 0.77 [0.83–0.61]; cut-off value 30 mm) and decreased RV ejection fraction (Hazard ratio 0.93, 95% Confidence Interval 0.87–0.99 per %; p = 0.03). Ventricular arrhythmia-free survival was reduced in patients with RVOT akinetic region length >30 mm (logrank p = 0.02).
Conclusion: RAAi predicts atrial arrhythmia and RVOT akinetic region length predicts ventricular arrhythmia in late follow-up of rtoF. These are simple, feasible measurements for inclusion in serial surveillance and risk stratification of rtoF patients.

1. Introduction

Repaired tetralogy of Fallot (rtoF) patients are a growing population at risk of right ventricular (RV) dilatation and dysfunction, atrial and ventricular tachyarrhythmias and sudden cardiac death during late follow-up [1–6]. The onset of atrial or ventricular arrhythmia in this population is associated with significant morbidity and death making prediction of arrhythmia a clinical priority. Currently, risk stratification for sudden death in adults is mainly centred around

QRS duration and impaired left ventricular function [2,3,7–9]. Previous studies investigating an association between these and other parameters and clinical events have tended to be retrospective or cross-sectional [4,5,9–12]. Indications and optimal timing for treatments that may modify risk of arrhythmia, such as pulmonary valve replacement (PVR) [13–15], atrial ablation, and/or prophylactic automated internal cardiac defibrillator implantation, are still evolving [9,16–18]. Precise outcome prediction, however, remains difficult.

We therefore examined predictors of atrial and ventricular tachyarrhythmias in rtoF patients in a prospective, longitudinal study. In the sub-group of patients with RV restrictive physiology relatively reduced ventricular dilatation and better exercise capacity have been demonstrated compared with others [19]. Hence, we tested whether this subgroup behaved differently with regard to arrhythmia.

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   [1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2. Methods

2.1. Study design and clinical outcomes

Between 2002 and 2008, 154 rtoF patients underwent CMR and same day clinical evaluation as part of prospective clinical research approved by the local research ethics committee and patients gave written informed consent [20,21]. Pre-specified clinical endpoints of new-onset atrial or ventricular arrhythmia were collected during follow-up until December 2011. Hospital records are updated routinely by the national death registry, thus mortality was comprehensively collected. Patients with an episode of atrial tachyarrhythmia (AA) prior to the baseline clinical assessment were excluded from the analysis of new-onset arrhythmia and patients were excluded from further follow-up from the time of PVR given the propensity of intervention to alter cardiac morphology and function.

2.2. Definitions of clinical endpoints

New-onset AA was defined as clinically documented sustained atrial tachyarrhythmia (atrial flutter or fibrillation; paroxysmal or established). New-onset ventricular tachyarrhythmia (VA) was defined as sustained ventricular tachycardia (≥ 30 s), ventricular tachycardia associated with presyncope or syncope (loss of consciousness clinically consistent with cardiac cause) or ventricular fibrillation. Sudden cardiac death was defined as any death clinically presumed to be related to arrhythmia.

2.3. Baseline evaluation

All cardiovascular magnetic resonance (CMR) measurements were made blinded from the presence of arrhythmia. At recruitment all scans were conducted and analysed by the same observer (SVB-N; interscan intraobserver coefficient of variability: RVEF 1.5%/LVEF 2.1%) [22] to maximise reproducibility of measurements using a 1.5 T scanner (Siemens Sonata, Erlangen, Germany) following a standardised protocol as previously reported [20,21]. The contour of the right atrium (RA) was manually traced by a single observer (BB) in the four-chamber view excluding the RA appendage and the vena cavae at their junction with the RA. The maximum contoured area, just prior to atrioventricular valve opening, was chosen to quantify the RA maximal area indexed to body surface area (RAAi) (Fig. 1A). The akinetic area length was measured by a single observer (SBN) as we previously described [18]. The RV was imaged in at least three long axis as well as the short axis planes. The maximum linear extent of the non-contractile region was identified in one or more CMR planes throughout the cardiac cycle. It was usually best measured in the sagittal RVOT view (Fig. 1B).

Interobserver variability and intraobserver variability for RAAi and RVOT akinetic area length were tested in a sample of 20 patients by two observers (BB, AK or BB, SBN respectively) blinded to each other.

Mean QRS duration was analysed manually from standard 12-lead electrocardiograms.

Echocardiographic pulsed and continuous wave Doppler pulmonary flow velocities were digitally recorded by a single echocardiologist (WL) using a Hewlett Packard Sonos 7500 (Andover, Massachusetts, USA).

RV restrictive physiology was defined as laminar anterograde flow in the pulmonary artery in late diastole coinciding with atrial contraction and present throughout the respiratory cycle (the "a" wave) [19]. Measurements were made with simultaneous respiratory motion recordings as previously described [19,23,24]. Tricuspid regurgitation (TR) was graded according to the European Association of Echocardiography [25].

Peak oxygen uptake (peak VO$_2$, mL/min/m^2) was determined from baseline cardiopulmonary exercise testing using graded treadmill exercise until exhaustion.

The authors are solely responsible for the design and conduct of this study, analyses and its final contents.

2.4. Statistical methods

Continuous data are presented as mean $\pm$ standard deviation or median and interquartile range depending on the data distribution as tested with the Kolmogorov–Smirnov test. Comparisons between subgroups were performed by unpaired *T*-test, Mann–Whitney *U* test or Chi-square test as appropriate. Interobserver agreement and intraobserver agreement of CMR RAAi measurement were assessed by coefficient of variability. The relationship between variables and outcome was investigated by univariate and, where appropriate, multivariate Cox proportional-hazard analysis. The results of the Cox regression were further assessed using a non-parametric random survival forest (RSF) analysis based on a log-rank splitting rule and time dependent receiver operator curve (ROC) analysis based on Kaplan–Meier methodology (RSF and survival ROC package) [26]. Cut-off values were defined according to the Youden rule.

Patients were censored at the time of PVR. For all analyses a two-tailed probability value $p < 0.05$ was used as the cut-off for statistical significance. Analyses were performed using R version 2.13.2 (The R Foundation for Statistical Computing) and MedCalc 12.1.4.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Baseline patient characteristics

One-hundred-and-fifty-four patients were studied. Patient characteristics are summarised in Table 1. Median follow-up was 5.6 (4.6–7.0) years. Nine patients (6%) had already presented with AA and were therefore excluded from new-onset AA analysis and none had previous VA. There were no clinical endpoints of syncope or death during the included follow-up period. Forty-nine patients were excluded from follow-up from the time of PVR. At the end of the study period 3 deaths had occurred after PVR; two perioperative and one sudden cardiac death.

Interobserver reproducibility and intraobserver reproducibility were 7.9 $\pm$ 2% (0.4; 4.8 cm^2/m^2) and 5.3 $\pm$ 1.4% (-1.44; 4.2 cm^2/m^2) for the RAAi respectively; and 7.4 $\pm$ 2.5% (-7.7; 6.7 mm) and 4.4 $\pm$ 1.5% (-4.5; 3.9 mm) for the akinetic region length respectively.

3.2. Predictors of atrial arrhythmia

Eleven AAs (7%) occurred in follow-up. Eight of 11 patients developed sustained atrial tachycardia, 7 of whom underwent subsequent atrial ablation procedures documenting 6 isthmus-dependent atrial flutters (5 counter-clockwise and 1 clockwise) and 2 other scar-related atrial tachycardias. The remaining 3 patients developed permanent atrial fibrillation. Patients who developed AA had a larger RAAi (16.6 [14.8–19.9] vs. 13.6 [11.9–15.2] cm^2/m^2; p = 0.0006), were older
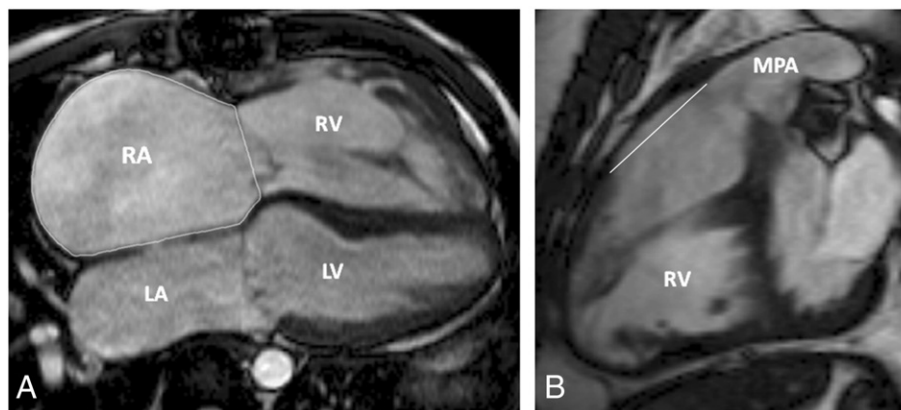

Fig. 1. Measurement of maximal RAAi (A) and RVOT akinetic region length (B). Measurements were made from balanced steady state free precession cine images. A shows an enlarged RA (33 cm^2/m^2). B shows a 45 mm non-contractile thin RVOT akinetic length. Abbreviations: LA: left atrium, LV: left ventricle, MPA: main pulmonary artery, RA: right atrium, RV: right ventricle.

Table 1
Features of rtoF patients with new-onset atrial arrhythmias or sustained ventricular tachyarrhythmia.

	All patients; n = 154	Atrial arrhythmia; n = 11	Ventricular arrhythmia; n = 9
Age at initial CMR study, years	30.8 [21.9–40.2]	**45.0 [39.2–50.6]**[a]	**42.5 [34.9–50.2]**[b]
Male, n, %	87 (56)	6 (56)	6 (66)
Hypertension (BP > 140 systolic), n (%)	10 (6.5)	2 (18)	3 (33)
Previous palliation[c], n (%)	30 (20)	2 (18)	3 (33)
Age at repair, years	4.5 [2–8.3]	7.6 [5.4–19.4][b]	**12.8 [6.2–13.9]**[b]
Transannular patch, n (%)	89 (65)	8 (72)	4 (44)
RVOT infundibular patch, n (%)	31 (23)	1 (9)	3 (33)
Conduit repair	17 (12)	1 (9)	2 (22)
NYHA ≥II, n (%)	20 (13)	**4 (36)**[a]	2 (22)
QRS duration, ms	147 ± 24.6	153 ± 23	150.8 ± 29.8
QRS >180 ms, n (%)	9 (6)	1 (9)	2 (22)
PS, m/s	2 [1.5–2.6]	1.5 [1.4–2.3]	2 [1.4–3.3]
PRF, %	27.9 ± 17	20 ± 12.8	28.3 ± 15
Previous PVR, n (%)	32 (21)	2 (18)	0 (0)
Peak VO$_2$, % of predicted	75.6 [64–88]	71 [61–80]	74 [71–77]
VE/VCO$_2$ slope	29.7 [25–35]	34 [32–38]	34.4 [26.7–40.2]
Restrictive physiology, n (%)	38 (25)	6 (54) 0.05	3 (33)
More than mild TR, n (%)	14 (9)	**4 (36)**[a]	0
RAAi, cm^2/m^2	14 [12–15.4]	**16.6 [14.8–19.9]**[a]	14.6 [14–17]
RVEDVi, mL/m^2	127 [102–148]	130 [115–144]	154 [123–167]
RVESVi, mL/m^2	58 [45–75]	67.5 [60.9–76.2]	81 [59–94]
RVSVi, mL/m^2	66 [55–76]	71 [50–75]	59 [44–76]
RVEF, %	53 [47–58]	48 [43–54]	**42 [40–52]**[b]
RVOT akinetic region length, mm	30 [20–40]	40 [27–49]	**55 [34–60]**[a]
LVEDVi, mL/m^2	73 [64–85]	78 [66–96]	100 [69–112]
LVESVi, mL/m^2	26 [21–33]	26 [22–33]	41 [18–52]
LVSVi, mL/m^2	47 [41–56]	49 [40–57]	59 [39–62]
LVEF, %	64 [60–70]	63 [59–72]	62 [51–68]
LVEF <45%, n (%)	5 (3)	2 (18)[d]	1 (0.6)

Data are expressed as mean ± standard deviation or median [IQR] as appropriate. CMR: cardiac magnetic resonance imaging, ECG: electrocardiography, LVEDVi: left ventricular end-diastolic volume indexed, LVEF: left ventricular ejection fraction, LVESVi: left ventricular end-systolic volume indexed, LVSVi: left ventricular stroke volume indexed, n: number of patients, NYHA: New York Heart Association, PRF: pulmonary regurgitant fraction, PS: pulmonary stenosis, PVR: pulmonary valve replacement, RA: right atrium, RAAi: maximum right atrial area indexed, rtoF: repaired tetralogy of Fallot, RVEDVi: right ventricular end-diastolic volume indexed, RVEF: right ventricular ejection fraction, RVESVi: right ventricular end-systolic volume indexed, RVOT: right ventricular outflow tract, RVSVi: right ventricular stroke volume indexed, TR: tricuspid regurgitation, VT: ventricular tachycardia. Statistically significant results are formatted bold.

[a] Significant difference (p ≤ 0.01) between this subgroup and remaining patients.
[b] Significant difference (p < 0.05) between this subgroup and remaining patients.
[c] 19 previous Blalock–Taussig shunt, 8 previous Waterston shunt and 6 Brock procedures.
[d] Trend with p = 0.05 for difference between this subgroup and remaining patients.

(45.0 [39.2–50.6] vs. 29.1 [20.9–39.3] years; p = 0.0001), had a later repair (7.6 [5.4–19.4] vs. 4.4 [1.9–8.4] years; p = 0.02), were in worse functional class (New York Heart Association Class ≥II: 36 vs. 13%; p = 0.01) and more often had TR (>mild TR: 36 vs. 9%; p = 0.0006) (Table 1). RAAi, age at baseline, age at repair, and more than mild TR were significant predictors of AA on univariate Cox analysis and random survival forest analysis (Table 2, Fig. 2). In view of the number of events and number of univariate predictors, random survival forest analysis was chosen rather than multivariate stepwise regression Cox analysis and RAAi was the strongest predictor of new-onset AA (Fig. 2). On ROC analysis, a cut-off value of 16 cm^2/m^2 was found to predict new-onset AA with sensitivity and specificity of 66% and 86% respectively, with area under the curve (AUC) of 0.75, during a median follow-up of 5.6 years.

RAAi ≥16 cm^2/m^2 predicted reduced AA-free survival (logrank p = 0.0001) (Fig. 3A).

3.3. Restrictive physiology and atrial arrhythmia

Features of RV restrictive physiology in rtoF patients are summarised in Table 3. Restrictive RV physiology patients had a larger RA size (p = 0.02), were older (p = 0.03), had a later repair (p = 0.02), and more often had TR (>mild TR; p = 0.0002) compared with the remaining patients; these parameters were predictors of new-onset AA. There was a trend towards restrictive RV physiology itself relating to new-onset atrial tachyarrhythmia (p = 0.057). RAAi was correlated significantly with RV end-diastolic volume index (r = 0.4, p < 0.0001) and inversely with RV ejection fraction (r = −0.4, p < 0.0001).

3.4. Predictors of ventricular arrhythmia in follow-up

Nine (6%) patients had VA during follow-up. These patients consisted of 3 patients with syncope due to sustained ventricular tachycardia, 1 patient with witnessed presyncope due to ventricular tachycardia, 4 patients with haemodynamically tolerated sustained ventricular tachycardia >30 s and 1 patient presenting with out-of-hospital cardiac arrest with ventricular fibrillation requiring DC cardioversion. Patients who developed VA were older (42.5 [34.9–50.2] vs. 29 [21–40] years; p = 0.01), had a later repair (12.8 [6.2–13.9] vs. 4.4 [2–8] years; p = 0.02), larger akinetic RVOT region (length 55 [34–60] vs. 30 [20–40] mm; p = 0.002) and a lower RV ejection fraction (42 [40–52] vs. 53 [51–55] %; p = 0.01) (Table 1). On univariate Cox analysis, only the RVOT akinetic region length and RV ejection fraction were predictive of VA (Table 2). On stepwise Cox regression analysis, the RVOT akinetic region length was the only remaining predictor of VA (Hazard ratio 1.05, 95% Confidence Interval 1.01–1.08 per mm; p = 0.004). The survival ROC curve analysis indicated a cut-off value of 30 mm as a predictor of VA during a median follow-up of 5.6 years with AUC of 0.77, sensitivity of 83% and specificity of 61%.

RVOT akinetic area length >30 mm predicted reduced VA-free survival (logrank p = 0.02) (Fig. 3B).

4. Discussion

To our knowledge this is the first prospective, longitudinal clinical study demonstrating the predictive value of RA size and RVOT morphology for atrial and ventricular tachyarrhythmias in adults with

Table 2
Univariate Cox analysis for new-onset atrial or ventricular tachyarrhythmia.

	Atrial arrhythmia; n = 11			Ventricular arrhythmia; n = 9		
	HR	95% CI	p	HR	95% CI	p
Age at initial CMR study, years	1.07	1.03–1.12	**0.0004**	1.04	0.99–1.09	NS
Age at repair, years	1.07	1.02–1.12	**0.002**	1.04	0.97–1.1	NS
Prior cardiac surgery, n	0.79	0.34–1.8	NS	1.40	0.57–3.49	NS
QRS duration, ms	1.01	0.98–1.03	NS	1.01	0.97–1.03	NS
PS Vmax, m/s	0.66	0.24–1.78	NS	1.30	0.58–3.17	NS
PRF, %	0.97	0.94–1.006	NS	0.99	0.95–1.03	NS
Peak VO$_2$, mL/kg/min	0.99	0.96–1.01	NS	0.99	0.96–1.02	NS
RAAi, cm^2/m^2	1.17	1.07–1.28	**0.0005**	1.00	0.99–1.002	NS
TR > mild, n	6.7	1.9–22.9	**0.002**	–	–	–
Restrictive RV	3.3	1.01–10.8	**0.04**	1.10	0.26–4.49	NS
RVEDVi, mL/m^2	1.002	0.98–1.01	NS	1.01	0.99–1.02	NS
RVESVi, mL/m^2	1.005	0.98–1.02	NS	1.01	0.99–1.02	NS
RVEF, %	0.95	0.9–1.01	NS	0.93	0.87–0.99	**0.03**
Akinetic region length, mm	1.01	0.98–1.05	NS	1.05	1.01–1.09	**0.003**
RVMi, g/m^2	0.96	0.90–1.01	NS	1.01	0.99–1.04	NS
LVEDVi, mL/m^2	1.01	0.98–1.04	NS	1.02	0.99–1.05	NS
LVEF, %	0.98	0.92–1.03	NS	0.96	0.90–1.03	NS
LVSVi, mL/m^2	0.99	0.94–1.05	NS	1.03	0.97–1.09	NS

CI: Confidence Interval, CMR: cardiovascular magnetic resonance, HR: hazard ratio, LVEDVi: left ventricle volume indexed, LVEF: left ventricle ejection fraction, LVSVi: left ventricular stroke volume indexed, PRF: pulmonary regurgitant fraction, PS V max: pulmonary stenosis peak velocity, RAAi: maximal right atrial area indexed, RVEDVi: right ventricular end-diastolic volume, RVEF: right ventricular ejection fraction, RVESVi: right ventricular end-systolic volume, RVSVi: right ventricular stroke volume indexed, LVSVi: left ventricular stroke volume indexed, n: number of patients, RVEF: right ventricular ejection fraction, RVMi: right ventricular mass indexed, VT: TR: tricuspid regurgitation, ventricular tachycardia, (–): insufficient data for appropriate analysis. Statistically significant p values are formatted bold.

rtoF. Previous studies, including those with CMR characterisation, are retrospective or cross-sectional [20,27–29]. RA dilatation was highly predictive of AA onset and more strongly predictive than older age, later repair or TR. Restrictive RV physiology was associated with older age, later repair, TR and larger RA, all of which in turn were associated with AA. VA was predicted by RVOT akinetic area length and impaired RV ejection fraction and independently predicted only by larger RVOT akinetic region. Atrial chamber enlargement and ventricular chamber enlargement are known drivers of adverse cardiac remodelling and arrhythmogenesis for the left heart [30]. Our study demonstrated that right-sided morphology is predictive of clinical arrhythmia, both atrial and ventricular, after rtoF.

4.1. Atrial tachyarrhythmia and relations to right atrial dilatation

RAAi is a feasible measurement during periodic follow-up, had acceptable variability and was a strong predictor of outcome in rtoF patients. A cut-off value of 16 cm^2/m^2 was predictive of AA.
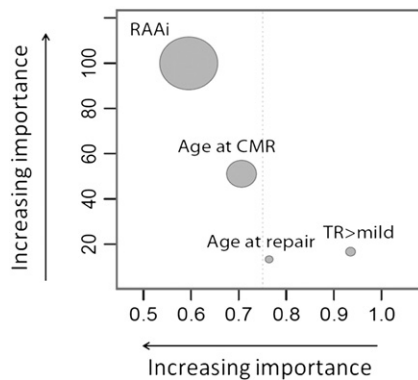

Fig. 2. Random survival forest analysis for predictors of atrial tachyarrhythmia. The relative importance of RAAi, age at the index CMR study, increased age at repair and the presence of more than mild TR for AA prediction during a median follow-up of 5.6 years is shown. The upper and leftward location in the plot of RAAi illustrates its greater relative importance and the size of the circle the larger effect size. The dashed line is the cut-off for relevant predictors. Abbreviations: CMR: cardiac magnetic resonance imaging, RAAi: right atrium area indexed, TR: tricuspid regurgitation.

A 7% incidence of AA was seen in our study at a median age of 45 [39.2–50.6] years over a median follow-up period of 5.6 years. Prevalence of AA has been reported to increase exponentially with age after a relatively quiescent period of 10 to 15 years [1] and in rtoF patients is associated with a high morbidity [2]. By the end of our study follow-up there was 13% prevalence of atrial arrhythmia in keeping with other studies [1,2]. Patients who developed AA in our study were older with median age 45 years. Older age and later age at repair have also been consistently noted as risk factors for atrial arrhythmias in previous studies [1,2,5,20,29].

Additionally, RA enlargement was a stronger predictor of new-onset AA than age or late repair in this study in which RA dilatation pre-dated atrial rhythm disturbance. Whether atrial dilatation is a cause or a consequence of rhythm disturbance has been debated [31]. Dilatation of atrial chambers is a well-understood determinant of AA propensity as it causes atrial stretch and consequent atrial electrical remodelling [31,32]. In rtoF, RA dilatation and dysfunction relate to chronic pressure or volume overload as well as previous intracardiac surgery involving surgical atriotomy and potentially progressive atrial myocardial fibrosis. RA distension may trigger atrial tachycardia relating to surgical atrial scar. In a previous large, retrospective study of 793 rtoF patients, TR was reported to be predictive of AA, presumably relating to resultant RA dilatation leading to arrhythmogenesis [2]. Detailed data regarding atrial substrates were not available for that cohort. RA enlargement discretely categorised as present or absent was also suggested to be a marker for atrial tachycardia by other investigators, though again detailed atrial characterisation was unavailable [1,33]. Whilst TR and RA dilatation are related to each other, and TR clearly predisposes to atrial arrhythmia, our study showed that RA enlargement predicted atrial arrhythmia more strongly than TR.

Reverse remodelling of the left atrium with intervention is associated with reduction in the risk of subsequent AA [34]. Future studies are needed to address the potential for reverse RA remodeling with ageing and with late intervention.

4.2. RV restrictive physiology, RA and RV dilatation

In contrast to the younger patients in previous reports [19] restrictive RV physiology rtoF patients had similar degree of RV dilatation, cardiopulmonary exercise capacity, pulmonary regurgitation and QRS
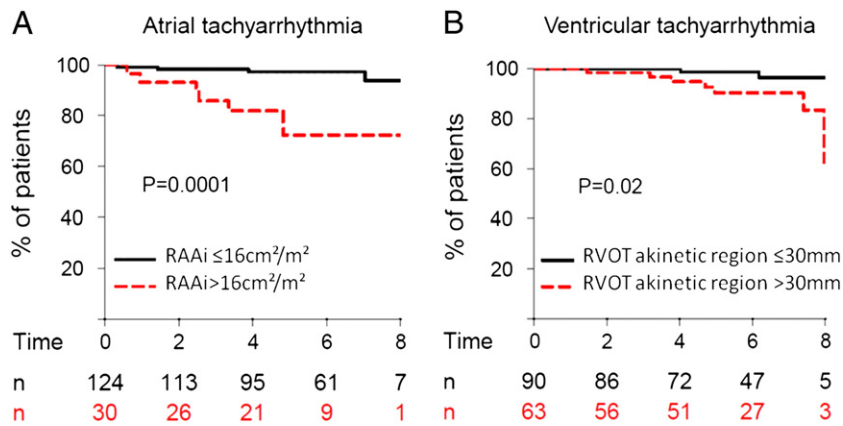
Fig. 3. Kaplan–Meier curves illustrating freedom from atrial (A) and ventricular (B) tachyarrhythmias. A shows the time-to-atrial arrhythmia with respect to a RAAi cut-off value of 16 cm^2/m^2. B shows the time-to-ventricular arrhythmia with respect to a RVOT akinetic region length cut-off value of 30 mm. Abbreviations: n: number of patients, RAAi: maximal right atrium area indexed, RVOT: right ventricular outflow tract.

duration than the remaining patients. RV restrictive physiology was associated with increased RA size predisposing these patients to significant morbidity related to AA which was 3 times more common than in those without restrictive RV physiology. The finding of a restrictive RV physiology associated with large RV in older rtoF patients has 2 potential explanations. First, any "protective" effect of RV restrictive physiology against RV dilatation was then not sustained over a longer follow-up period. Alternatively, beyond a certain degree of RV dilatation any further filling became limited and a restrictive physiology pattern appeared.

4.3. Ventricular arrhythmia and RV infundibular disease

RVOT akinetic region length and decreased RV ejection fraction predicted ventricular arrhythmia in this study. Non-contractile RVOT regions contribute to decreased RVEF [20,27]. RVOT akinetic region length was independently predictive of VA during follow-up. RVOT akinetic regions have been associated with myocardial fibrosis or scarring (not necessarily related to surgical patching) [20] and electromechanical delay [35]. A significant proportion, though not all, of our patients underwent earlier era surgery with infundibular or transannular patch use at the time of repair. Yet, the RVOT akinetic regions seemed to relate to ongoing risk of arrhythmia. Suture line around the RVOT patch may vary in size and provide a perimeter between neighbouring prosthetic patch material and native RVOT which may be a potential nidus for progressive stretch, thinning and distension, ongoing myocardial fibrosis and arrhythmogenesis [20]. Furthermore, electromechanical delay in the RVOT contributes to total RV delay and prolongation of the QRS duration [35]. QRS duration prolongation, in turn, is a major risk factor for sudden cardiac death [2]. The source of ventricular tachycardia is most commonly the RVOT in rtoF [36,37]. The RV infundibulum in rtoF therefore plays a key role in determining the risk of developing clinical VT. There is further justification, therefore, for the recently modified surgical approaches to repair of tetralogy of Fallot which aim to limit the extent and depth of myocardial RVOT infundibular resection [38].

Table 3
Features of rtoF patients with RV restrictive physiology.

	Restrictive RV physiology n = 38	Non-restrictive RV physiology n = 110	p value
Age at initial CMR study, years	38 [26.1–45.0]	30.1 [20.2–39.7]	**0.03**
Age at repair, years	6.7 [3.8–12.8]	4.1 [1.9–8.4]	**0.02**
Transannular patch repair, n	23 (60)	62 (56)	NS
QRS duration, ms	146 ± 27	147 ± 23	NS
PS, m/s	2.1 [1.5–3]	2 [1.5–2.6]	NS
PRF, %	29.2 ± 14	27.8 ± 17	NS
Peak VO$_2$, % predicted	75.6 [64–89]	76 [62–88]	NS
Peak VO$_2$ achieved, mL/kg/min	26.1 [20–29]	27 [21–31]	NS
RAAi, cm^2/m^2	14.6 [12.7–16.6]	13.2 [11.7–15]	**0.02**
TR > mild, n (%)	8 (21)	4 (3)	**0.0002**
Atrial arrhythmia, n, new-onset (total)	6 (15)	5 (4.5)	0.057
Ventricular arrhythmia, n, new-onset (total)	3 (7)	6 (5)	NS
PVR, n, new-onset (total)	10 (26)	39 (35)	NS
RVEDVi, mL/m^2	125 [107–145]	126 [101–151]	NS
RVESVi, mL/m^2	59.6 [42–71]	56 [45–76]	NS
RVSVi, mL/m^2	65 [54–77]	66 [56–75]	NS
RVEF, %	53 [48–57]	53 [46–59]	NS
Akinetic region length, mm	30 [20–45]	30 [20–40]	NS
RVMi, g/m^2	55 ± 20	51 ± 14	NS
LVEDVi, mL/m^2	72 [59–93]	73 [65–84]	NS
LVSVi, mL/m^2	47 [39–53]	45 [41–56]	NS
LVEF, %	63 [58–70]	64 [60–70]	NS

Data are expressed as mean ± standard deviation, median [IQR] and number (%) as appropriate. Statistically significant p values are formatted bold.
LVEDVi: left ventricle end-diastolic volume indexed, LVEF: left ventricle ejection fraction, LVSVi: left ventricle stroke volume indexed, n: number of patients, PRF: pulmonary regurgitant fraction, PS: pulmonary stenosis, PVR: pulmonary valve replacement, RAAi: maximal right atrial area indexed to body surface area, RVEDVi: right ventricular end-diastolic volume indexed, RVEF: right ventricular ejection fraction, RVESVi: right ventricular end-systolic volume indexed, RVSVi: right ventricular stroke volume indexed, RVi mass: right ventricular mass indexed, TR: tricuspid regurgitation, VT: ventricular tachycardia.

Pulmonary regurgitation is a recognised risk factor for sustained ventricular tachycardia [2] that can be addressed with PVR. To what degree RVOT akinetic resection during PVR can further modify the risk of ventricular arrhythmia is still unclear. PVR associated with intraoperative cryoablation decreases the incidence of sustained ventricular tachycardia [13]. In a randomised trial of PVR with RVOT patch resection versus PVR with individualised more extensive RVOT scar resection, no additional RV remodelling was found at 6 months; longer follow-up would be required to determine a potential effect on VA propensity [39].

In contrast with previous studies, QRS duration > 180 ms, pulmonary regurgitation, and LV dysfunction did not predict sustained ventricular tachycardia in this study [1,4,5,7]. The majority of our patients had pulmonary regurgitation, right bundle branch block and a prolonged QRS duration (mean 150 ms) so a much longer period of observation may be required to detect different outcomes based on these results. Furthermore, potentially relevant markers of LV impairment more subtle than ejection fraction were not assessed. We do not therefore conclude that these factors are irrelevant. However, LV dysfunction may be a later phenomenon and be consequent to RV impairment due to ventricular–ventricular interaction [27,28]. Therefore, RV outflow tract and RV dysfunction may be of earlier prognostic value.

4.4. Study limitations

Congenital heart disease studies including ours are inherently small, the clinical event rate per year is relatively low and thus Cox regression analysis can be underpowered to detect all predictors. Random survival forest analysis has been shown to outperform parametric methods when sample sizes are small [40]. Despite relatively few events in long-term follow-up, this prospective study does have the advantage of comprehensive single-centre data collection and optimal study design for maximising CMR measurement reproducibility. A large multicentre trial or registry may validate our data and include the potential prognostic role of other factors such as electrophysiological studies and ablations [4] late gadolinium enhancement (LGE) CMR [20] or signal averaged ECG [41] not assessed here. Despite that the four-chamber cines were all acquired by the same operator and according to the same protocol, RAAi measurement may depend on the exact slice orientation. In the future, determination of RA volume using a contiguous atrial stack of transaxial or short axis cines might prove worthwhile. Our existing study approach however does allow feasible measurement from routine existing protocols without lengthening CMR duration.

Myocardial fibrosis demonstrated with LGE CMR may prove to be an important risk factor for tachyarrhythmia in rtoF as cross-sectionally more extensive RV LGE was shown to correlate with clinical arrhythmia presentation [20]. RVOT LGE corresponds to regional akinesia and could also be measured linearly in a further prospective study. Current rtoF patients have undergone modified surgical approaches, undergoing repair at an earlier age and having operations sparing the RVOT infundibulum [38]. Risk factors for younger adults and future adult patients may therefore differ from those reported in this population. Paced patients and those with primary prevention automated-internal-cardiac-defibrillator were not included in this study due to the need for CMR.

5. Conclusions

RA area enlargement is a strong predictor of atrial tachycardia during late follow-up of patients with rtoF. Larger RVOT akinetic region and impaired RVEF predict ventricular tachyarrhythmia. The RV infundibulum in rtoF plays a key role in determining the risk of ventricular arrhythmogenesis. These are newly described predictors of clinical outcome. Restrictive RV physiology predisposes to RA enlargement and thus to atrial arrhythmogenesis in follow-up. Whether changes in RA or RVOT anatomy and function from electrophysiological or surgical interventions can modulate the arrhythmic risk in these patients needs to be examined.

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