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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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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 ± 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 ± 2% (0.4; 4.8 cm^2/m^2) and 5.3 ± 1.4% (−1.44; 4.2 cm^2/m^2) for the RAAi respectively; and 7.4 ± 2.5% (−7.7; 6.7 mm) and 4.4 ± 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

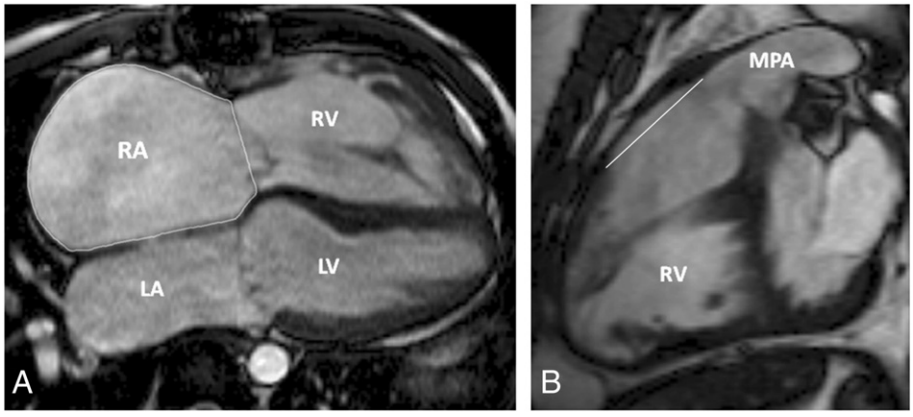

Fig. 1. Measurement of maximal RAAi (A) and RVOT akinetic region length (B). Measurements were made from balanced steady state free precession cine images. A shows an enlarged RA (33 cm^2/m^2). B shows a 45 mm non-contractile thin RVOT akinetic length. Abbreviations: LA: left atrium, LV: left ventricle,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