Right ventricular adaptation to chronic abnormal loading

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DOI:
10.33612/diss.135804654

7

Risk of cardiac tachyarrhythmia in patients with repaired tetralogy of Fallot: a multicenter cardiac MRI based study

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International Journal of Cardiovascular Imaging 2018;35:143-51

ABSTRACT

Background: Cardiac tachyarrhythmias are the leading cause of morbidity and mortality in patients with repaired tetralogy of Fallot (TOF). We evaluated risk factors for sustained ventricular tachyarrhythmia (VT) and atrial tachyarrhythmia (ATA) in these patients.

Methods: Patients (n = 319) who underwent cardiac magnetic resonance (CMR) imaging at two tertiary centers between 2007 and 2016 were assessed. Potential risk markers, based on history, cardiac magnetic resonance imaging (CMR), electrocardiography (ECG) and echocardiography, were analyzed for prediction of the primary endpoint of VT, and the secondary endpoint of ATA.

Results: During a follow-up of 3.5 (0.9–6.1) years, 20 (6.3%) patients reached the primary endpoint, and 30 (9.4%) the secondary endpoint. Multivariable cox hazards regression identified right ventricular (RV) end-diastolic volume (Hazard ratio [HR] 2.03, per 10 ml/m2 increase; p = 0.02), RV end-systolic volume (HR 3.04, per 10 ml/m2 increase; p = 0.04), RV mass (HR 1.88, per 10 g/m2 increase; p = 0.02), and RV ejection fraction (HR 6.06, per 10% decrease; p = 0.02) derived from CMR to be independent risk factors of VT. In addition, QRS-duration (HR 1.70, per 10 ms increase; p = 0.001) and body mass index (BMI: HR 1.8, per 5 kg/m2 increase; p = 0.02) were independent markers of VT. Older age at TOF repair (HR 1.33, per 2 months increase; p = 0.03) and BMI (HR 1.76, per 5 kg/m2 increase; p < 0.001) independently predicted ATA.

Conclusion: RV systolic dysfunction, hypertrophy and dilatation on CMR, together with QRS prolongation, and obesity are predictive of VT in TOF patients. Older age at TOF repair and obesity were associated with the occurrence of ATA.

INTRODUCTION

The life expectancy of patients with tetralogy of Fallot (TOF) has increased substantially over time due to advanced management and therapeutic options [1, 2]. However, residual anatomic cardiac anomalies and surgical sequels are a common phenomenon, which may result in long-term morbidity and mortality [3, 4]. With the raising life expectancy of repaired TOF patients, adequate monitoring and valuing of late detrimental impact of the disease becomes increasingly relevant.

Repaired TOF patients may develop conduction disturbances, such as ventricular tachyarrhythmia (VT) and atrial tachyarrythmia. These conduction disturbances often result in substantial morbidity or—although uncommon— may lead to sudden cardiac death (SCD) [5]. Adequate and timely prediction of these cardiac events enhances treatment strategy in these patients, such as implantation of an implantable cardioverter defibrillator (ICD) implantation. In current clinical practice, echocardiography, electrocardiography (ECG) and cardiac magnetic resonance imaging (CMR) are essential diagnostic tools for monitoring patients with repaired TOF [6–9]. These tools are important since cardiac morphology and function can be assessed over time providing prognostic information which may contribute to the decision-making of cardiac interventions [8–10].

Aggressive management of suspected or reported atrial and ventricular cardiac arrhythmias is often considered to improve functional outcome and prevent relapse of these adverse events. ICD therapy is currently the most aggressive and preferred treatment for secondary prevention of sustained VT or cardiac arrest. Yet, there are currently no class I indication treatment strategies for primary prevention in these patients. The value of the available diagnostic tools to predict life-threatening events, still warrants further investigation.

Therefore, to aid clinical outcome and decision-making, we sought to define risk factors for cardiac tachyarrhythmia in children and adults with repaired TOF in a large multicenter cohort.

METHODS

In this retrospective multi-center study, we identified consecutive patients, both adults and children, with repaired TOF who underwent routine CMR between January 2007 and May 2016 at two tertiary centers (i.e. Stanford University Medical Center [SUMC], California, USA, and University Medical Center Groningen [UMCG], the Netherlands). If a patient has undergone more than one CMR, the first CMR that was performed between 2007 and 2016 was used for analysis. TOF patients with major residual and confounding structural

intra-cardiac disease (i.e. pulmonary atresia, absent pulmonary valve and partial anomalous pulmonary venous return) were excluded. Patients with claustrophobia and patients with insufficient CMR image quality (i.e. artifacts or velocity aliasing) were also excluded. In addition, we excluded patients who were lost to follow-up. Demographic data (i.e. age, sex and body surface area) and surgical history (i.e. date and type of initial repair, palliative shunt if any, and any re-interventions) were extracted from the medical records. This study was approved by each participating site's Medical Ethical Review Board. All assessments used in the current study were performed in the setting of regular care for these patients. Because of the retrospective character of the study, the need for individual informed consent was waived.

Cardiac magnetic resonance imaging protocol

CMR assessments were performed either on a 1.5-T scanner at the UMCG (Siemens, Erlangen, Germany, SUMC and LPCG; Signa TwinSpeed, Signa 450-w) or a 3 T MR scanner at SUMC (Signa 750, GE Healthcare, Wisconsin, the United States). A retrospectively gated steady-state freeprecession (SSFP) sequence was used to obtain ECG-gated cine loop images with breath holding. The four-chamber view was used for long-axis slices and short-axis slices were subsequently acquired covering both ventricles from base to apex. To help define positions of the tricuspid and mitral valves, additional SSFP cine images were taken in the long axis planes. All non-sedated patients were instructed to hold their breath during the examinations, and the images were acquired during end-expiratory breath holds. Two-dimensional velocity encoded CMR flow measurements, perpendicular and ± 1.5 cm cranial to the pulmonary valve, were performed using 2-D gradient echo Fast Low Angle Shot (FLASH), acquired during normal respiration with retrospective cardiac gating.

Cardiac magnetic resonance imaging analysis

All CMR studies were analyzed offline using available software (QMass 7.6, Medis, Leiden, The Netherlands) to quantify right and left ventricular function, volume and mass. The assessments were performed by three observers (T.M.G, N.E.G. and Q.A.J) and if deemed necessary, reviewed by two radiologists (T.P.W. and F.P.C.). The short-axis endoand epicardial borders of the left ventricle (LV) followed by the right ventricle (RV) were manually traced in end-diastolic and end-systolic phases, according to post-processing guidelines of the Society for Cardiovascular Magnetic Resonance. On the most basal slice, both atria, the aorta and the pulmonary artery were excluded. The right ventricular outflow tract was included until the pulmonary valve. As described previously, the papillary muscle and trabeculae were excluded from RV and LV blood volume, by using semi-automatic threshold-based segmentation software (MassK Mode®, Medis, Leiden, The Netherlands). (Fig. 1) [11] RV and LV end-systolic and end-diastolic volumes and mass were automatically generated by the summation of slice areas multiplied by slice thickness. Stroke volume (SV), ejection fraction (EF), RV/ LV volume and mass ratio and RV

mass/volume ratio were calculated using standard formulas. Analyses of pulmonary flow were analyzed using QFlow 5.6 (Medis, Leiden, The Netherlands). Pulmonary artery contours were generated semi-automatically on the standard magnitude images, and thereafter manually adjusted for each phase image. Post-processing automated background offset correction is an integral part of QFlow 5.6 and was performed for each case based on previous experience [12]. Pulmonary forward flow and regurgitant flow were measured and used to calculate cardiac output (CO) and pulmonary regurgitant fraction using standard formulas. All absolute volumes and masses were indexed for body surface area (BSA) using the calculation of Haycock [13].

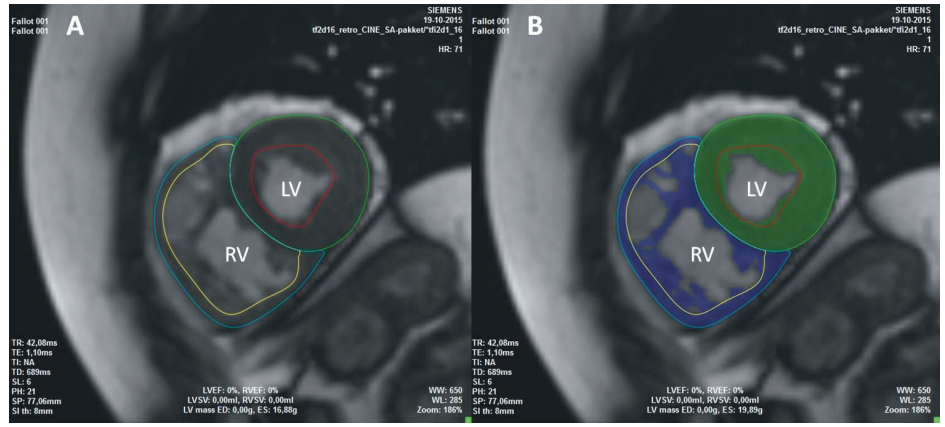

Figure 1 | Short-axis CMR image of a patient with repaired tetralogy of Fallot. a The blue line represents the epicardial border and the yellow line the endocardial border of the RV. b Using semi-automatic threshold-based segmentation, papillary muscle and trabeculae within in the endocardial contour (i.e., yellow line) are included in the RV mass (i.e., blue shade)

Echocardiographic protocol

Echocardiographic studies were performed on commercially available machines according to standardized local protocols. Variables of the echocardiographic study closest to the CMR, and only if performed within 3 months from the CMR study, were extracted from echocardiographic reports. The pulmonary valve (PV) peak gradient was calculated from the maximal pulmonary velocity jet, using the simplified Bernoulli equation: 4v2. The severity of pressure load on the RV was categorized into three groups: mild (PV peak gradient < 36 mmHg), moderate (PV peak gradient 36–64 mmHg) and severe (PV peak gradient ≥ 64 mmHg). For determining the severity of tricuspid regurgitation (TR), color flow Doppler, pulsed wave Doppler, continuous wave Doppler, vena contracta diameter, peak tricuspid systolic inflow and hepatic flow were used and TR was graded as absent/trivial (grade 0), mild (grade 1), moderate (grade 2) and severe (grade 3). In addition, any residual atrial septal defects and/or ventricular septal defects were reported.

Electrocardiographic protocol

QRS duration was measured on standard 12-lead ECGs. The ECG closest to CMR was extracted from the medical records and was only used when performed within 3 months from the CMR study.

Outcomes

Outcomes were extracted from medical records from January 2007 until May 2016. The primary outcome measure was the occurrence of VT, determined as a documented episode on a 12-lead ECG or holter recording of sustained VT ≥ 30 s, sudden cardiac arrest survivor (i.e. documented and needed resuscitation), symptomatic VT requiring an ICD implantation or appropriate ICD shock (i.e. triggered by VT or VF documented by stored intracardiac electrogram). Patients with more than one event (e.g. appropriate ICD shock after sustained VT) were categorized according to the first event. The secondary outcome measure was the occurrence of sustained atrial tachyarrhythmia, defined as intra-atrial re-entrant tachycardia, including typical atrial flutter, atrial fibrillation and other types of supraventricular tachycardia (e.g. atrioventricular nodal reentrant tachycardia, accessory pathway mediated tachycardia and ectopic atrial tachycardia) derived from 12-lead ECG and holter recordings.

Statistical analysis

Data were presented as numbers and percentages, mean ± standard deviation (SD) and median (interquartile range). According to their distribution, continuous variables of subgroups were compared using independent samples t-test or Mann–Whitney U test. Categorical variables of subgroups were compared using Chi-squared test or Wilcoxon signed rank test. Pearson correlation or Spearman rank correlation were used for bivariate correlations, according to distribution.

Follow-up time was defined as time from CMR to either an endpoint, or in the absence of an endpoint the date of the last-follow-up record. All variables with a p-value less than 0.1 were included in the multivariable stepwise backward regression analysis selection model. For RV mass, a receiver operator characteristic (ROC) curve was plotted. The optimal cut-off value for RV mass was determined, with highest sensitivity and specificity.

For the determination of the inter-observer variability of CMR analysis, two fully blinded observers (N.E.G. and Q.A.J.) analyzed ten randomly selected CMR studies. 20 randomly selected CMR studies were used for assessment of intra-observer variability of CMR analysis, performed by one observer (N.E.G.), who was blinded for the clinical, CMR, ECG and echocardiographic variables. The interval between the intra- and inter-observer analyses was more than three months. The Two-way mixed Intraclass Correlation Coefficient was used.

Statistical significance was considered achieved at a p-value < 0.05. All statistical analyses were performed using SPSS (Version 23, 2015).

RESULTS

Study population

Figure 2 displays the flow chart of in- and exclusion of patients in the study. In total, 423 CMR studies in patients with repaired TOF were identified. Of these, 50 patients with confounding intra-cardiac defects were excluded, as well as 15 patients with insufficient CMR quality, and six cases due to claustrophobia. Furthermore, 33 patients with incomplete clinical data were excluded, leaving a final amount of 319 unique patients. Baseline characteristics of these patients are summarized in Table 1.

The median time between TOF repair and CMR was 23 (IQR 15–31) years. In 318 patients (99%) Doppler echocardiographic quality was sufficient to obtain tricuspid regurgitation velocity and severity and pulmonary valve peak gradient. The median interval between the echocardiographic assessment and CMR was − 24 (IQR − 72 to [− 14]) days. In 315 patients (99%), ECG data was available for analysis. The median time between ECG and CMR was − 11 (IQ: − 45 to [− 33]) days.

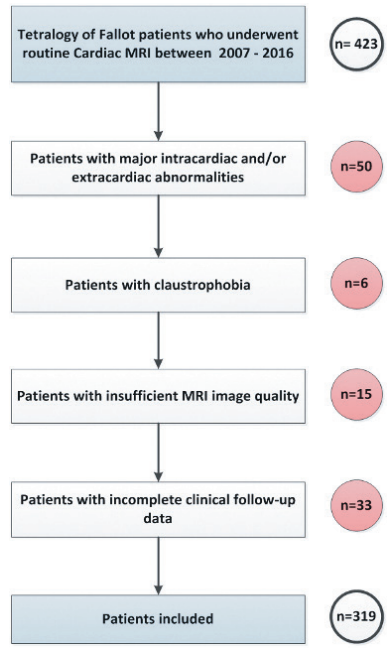

Figure 2 | Flowchart of the study population

Outcomes

Ventricular tachyarrhythmia

During a median follow-up of 3.5 (0.9–6.1) years, a total of 20 (6.3%) patients reached the primary endpoint of VT (median age 43 [IQR 34–53] years) of whom nine patients experienced documented VT ≥ 30 s, four were cardiac-arrest survivors, five underwent ICD implantation for symptomatic VT and two had an appropriate ICD shock after ICD implantation for primary prevention. There were no sudden cardiac deaths. Three patients died of non-cardiac cause and one patient died of unknown cause. Death was not included as event in the analyses.

Table 1 | Baseline characteristics of the study population.

Demographics	**Total n=319**	**Cardiac magnetic resonance imaging**	**n=319**
Sex, male	156 (49.0%)	RV mass index (g/m^2)	40.1 ± 10.3
Age, years	24 (15-36)	RV end-diastolic volume index (ml/m^2)	122 ± 35.6
Body mass index, kg/m^2	22.8 ± 5.52	RV end-systolic volume index (ml/m^2)	61.5 ± 22.5
Body surface area, m^2	1.66 ± 0.39	RV stroke volume index (ml/m^2)	60.4 ± 18.3
Surgical history		RV ejection fraction (%)	49.9 ± 7.85
Shunt	76 (23.8%)	RV/LV volume ratio	1.62 ± 0.47
Shunt type		RV mass/volume ratio	0.35 ± 0.09
Blalock–Thomas–Taussig	62 (19.4%)	LV mass index (g/m^2)	54.3 ± 15.2
Waterston	7 (2%)	LV end-diastolic volume index (ml/m^2)	77.1 ± 18.3
Aorta pulmonary	4 (1%)	LV end-systolic volume index (ml/m^2)	32.8 ± 11.3
Other	3 (0.3%)	LV stroke volume index (ml/m^2)	44.3 ± 20.8
Age at initial correction (years)	1.29 (0.9 – 4.7)	LV ejection fraction (%)	57.9 ± 8.34
Time TOF repair to CMR (years)	23 (15 – 31)	Pulmonary regurgitation fraction (%)	27.1 ± 17.2
Correction type		**Echocardiography**	**n=318**
Transannular patch	185 (58%)	Pulmonary valve peak gradient (mmHg)	22.8 ± 15.4
no-Transannular patch	51 (16%)	Tricuspid regurgitation (≥moderate)	43 (8.1%)
Conduit	12 (4%)	**Electrocardiography**	**n=315**
Unknown	69 (22%)	QRS duration	144 (122 -158)

Variables are expressed as n (%), mean ± standard deviation or median (interquartile range) LV left ventricular, RV right ventricular

Several demographic, CMR, electrocardiographic and echocardiographic variables were associated with the primary outcome in the univariate Cox-proportional Hazard regression analysis, as can be seen in Table 2. In the multivariable Cox-proportional Hazard regression analysis, the CMR variables RV end-diastolic volume (HR 2.03, per 10 ml/m^2 increase; 95% confidence interval [CI] 1.11–3.69; p = 0.02), RV end-systolic volume (HR 3.04, per 10 ml/m^2 increase; 95% CI 1.04–8.94; p = 0.04) and RV mass (HR 1.88, per 10 g/m^2 increase; 95% CI 1.11–3.18; p = 0.02), together with RV ejection fraction (HR 6.06, per 10% decrease; 95% CI 1.36–16.9; p = 0.02) were predictive of VT. QRS-duration (HR 1.70, per 10 ms increase; 95% CI 1.25–2.31; p = 0.001) on ECG, and BMI (HR 1.8, per 5 kg/m^2 increase; 95% CI 1.1–3.07; p = 0.02) were independent predictors of VT. The optimal cut-off value for RV mass was 50 g/m^2 (sensitivity 63%, specificity 83%).

Atrial tachyarrhythmia

A total of 30 (9.4%) patients (median age 44 [IQR 35–51] years) reached the secondary endpoint of atrial tachyarrhythmia, of whom 16 had intra-atrial re-entrant tachycardia, three had atrial fibrillation, nine experienced other types of supraventricular tachycardia and two had a combination of atrial fibrillation, intra-atrial re-entrant tachycardia and/or supraventricular tachycardia. Univariate associated risk factors for atrial tachyarrhythmia are displayed in Table 3. In the multivariate analysis, BMI (HR 1.76, per 5 kg/m2; 95% CI 1.23–2.49; p ≤ 0.001), and older age at TOF repair (HR 1.32, per 2 month increase; 95% CI 1.04–1.69; p = 0.03) were independently predictive of the secondary outcome.

Intra- and interclass correlation

For the inter-observer measurements, the correlation for LV end-diastolic volume was 0.80 (95% CI 0.21–0.95, p = 0.01), for LV end-systolic volume was 0.84 (95% CI 0.34–0.95, p = 0.006), for LV mass was 0.91 (95% CI 0.85–0.99, p < 0.001), for RV end-diastolic volume was 0.91 (95% CI 0.64–0.98, p = 0.001), for RV end-systolic volume was 0.94 (95% CI 0.79–0.99, p < 0.001), for RV mass was 0.92 (95% CI 0.66–0.98, p = 0.001) and for pulmonary regurgitation fraction was 0.93 (95% CI 0.82–0.97, p < 0.001). The intraclass correlation for the intra-observer variability for RV end-diastolic volume, RV end-systolic volume, and RV mass was 0.93 (95% CI 0.79–0.94, p < 0.001), 0.93 (95% CI 0.78–0.94, p < 0.006) and 0.92 (95% CI 0.80–0.96, p < 0.001), respectively. For the intra-observer measurements of the left ventricle, the correlation for LV end-diastolic volume was 0.95 (95% CI 0.92–0.99, p < 0.001), for LV endsystolic volume 0.94 (95% CI 0.90–0.98, p < 0.007), and for LV mass the correlation was 0.93 (95% CI 0.86–0.98, p < 0.001). The intra-observer intraclass correlation for pulmonary regurgitation fraction was 0.97 (95% CI 0.92–0.98, p < 0.001).

Table 2 | Cox proportional hazard analysis for ventricular tachycardia.

Univariable analysis			
Demographic variables	**Hazard Ratio**	**95% CI**	**P Value**
Sex, male	6.14	1.78-21.1	**0.004**
Age at CMR	1.05	1.02-1.08	**0.001**
BMI	1.09	1.02-1.19	**0.01**
Surgical History			
Age at TOF correction	1.06	1.02-1.11	**0.008**
Shunt	2.59	0.59-11.3	0.20
Cardiac MRI variables			
RV end diastolic volume	1.01	1.00-1.02	**0.05**
RV end systolic volume	1.03	1.01-1.05	**0.003**
RV stroke volume	0.92	0.97-1.03	0.92
RV mass	1.09	1.05-1.13	**<0.001**
RV ejection fraction	0.89	0.84-0.95	**<0.001**
RV cardiac output	1.14	0.98-1.32	0.08
Ratio RV/LV volume	2.85	1.25-6.52	**0.01**
LV end diastolic volume	1.00	0,98-1.03	0.79
LV end systolic volume	1.02	0.98-1.06	0.22
LV stroke volume	1.01	0.96-1.05	0.84
LV mass	1.04	1.01-1.06	**0.001**
LV ejection fraction	0.97	0.93-1.02	0.29
LV cardiac output	1.18	0.87-1.59	0.28
Pulmonary regurgitation fraction	1.02	0.99-1.05	0.14
ECG variables			
QRS-duration	1.06	1.04-1.09	**<0.001**
Echocardiographic variables			
PV peak gradient	1.01	0.99-1.04	0.31
≥ moderate TR	0.27	0.09-0.76	**0.006**

Multivariable Cox proportional hazard model			
	Hazard Ratio	**95% CI**	**P Value**
BMI (per 5 kg/m^2 increase)	1.8	1.1 – 3.07	**0.02**
RV end-diastolic volume (per 10 ml/ m^2 increase)	2.03	1.11-3.69	**0.02**
RV end-systolic volume (per 10 ml / m^2 decrease)	3.04	1.04-8.94	**0.04**
RV ejection fraction (per 10 % decrease)	6.06	1.36 - 16.9	**0.02**
RV mass (per 10 g/ m^2 increase)	1.88	1.11-3.18	**0.02**
QRS-duration (per 10ms increase)	1.70	1.25-2.31	**0.001**

CI confidence interval, BMI body mass index, CMR cardiac magnetic resonance imaging, ECG electrocardiography, LV left ventricle, PV pulmonary valve, RV right ventricle, TOF tetralogy of Fallot, TR tricuspid regurgitation Significant p values (<0.05) are bold

Table 3 | Cox proportional hazard analysis for atrial tachyarrhythmia.

Univariable analysis			
Demographic variables	**Hazard Ratio**	**95% CI**	**P Value**
Sex, male	0.74	0.33-1.63	0.46
Age at CMR	1.06	1.04-1.09	**0.001**
BMI	1.11	1.05-1.19	**<0.001**
Surgical History			
Age at TOF correction	1.06	1.02-1.11	**0.002**
Shunt	0.82	0.34-1.96	0.66
Cardiac MRI variables			
RV end diastolic volume	0.99	0.98-1.00	0.56
RV end systolic volume	1.00	0.98-1.02	0.82
RV stroke volume	0.98	0.96-1.00	0.15
RV mass	1.01	0.97-1.05	0.57
RV ejection fraction	0.95	0.91-1.01	0.09
RV cardiac output	0.96	0.75-1.24	0.77
Ratio RV/LV volume	1.58	0.71-3.53	0.26
LV end diastolic volume	0.99	0.96-1.01	0.24
LV end systolic volume	0.99	0.96-1.03	0.73
LV stroke volume	0.96	0.92-0.99	**0.04**
LV mass	1.00	0.98-1.03	0.74
LV ejection fraction	0.97	0.93-1.02	0.16
LV cardiac output	0.78	0.54-1.15	0.22
Pulmonary regurgitation fraction	0.98	0.96-1.01	0.27
ECG variables			
QRS-duration	1.01	0.99-1.02	0.54
Echocardiographic variables			
PV peak gradient	0.99	0.96-1.03	0.80
≥ moderate TR	0.79	0.23-2.67	0.71

Multivariable Cox proportional hazard model			
	Hazard Ratio	**95% CI**	**P Value**
BMI (per 5 kg/m^2 increase)	1.76	1.23-2.49	**0.001**
TOF correction age (per 2 months increase)	1.33	1.04-1.69	**0.03**

CI confidence interval, BMI body mass index, CMR cardiac magnetic resonance imaging, ECG electrocardiography, LV left ventricle, PV pulmonary valve, RV right ventricle, SD standard deviation, TOF tetralogy of Fallot, TR tricuspid regurgitation Significant p values (<0.05) are bold

DISCUSSION

The present study demonstrated that CMR derived RV volumes, mass and ejection fraction predict the occurrence of VT in patients with repaired TOF. In addition, prolonged QRS duration on ECG, and higher BMI were associated with VT development over time. We further observed that older age at TOF repair and higher BMI were independent predictors of atrial tachyarrhythmia in this cohort. Our study represents the only study thus far to describe BMI as independent predictor of sustained VT and atrial tachyarrhythmia development in these patients.

Multiple evaluations of potential risk factors for the occurrence of cardiac arrhythmias and SCD in patients with repaired TOF have been conducted [5–7]. Surgical history, clinical symptoms, QRS-duration and residual anatomic cardiac anomalies have been consequently reported as risk markers for these adverse events [10]. Therapeutic interventions are based on these risk markers. There is a class I indication for ICD therapy for secondary prevention after ventricular fibrillation or hemodynamic unstable VT. The decision for ICD implantation for primary prevention is challenging and should be made in a multidisciplinary setting. ICD therapy may protect TOF patients for future VT, ventricular fibrillation and SCD. On the other hand, implanting cardiologists should consider potential overtreatment in primary ICD implantation, since these interventions are associated with significant rates of complications, such as infection and inappropriate shocks. Suggested indications for ICD implantation, although inconsistent, are: an history of syncope, non-sustained VT and palliative shunts, late timing of TOF repair, ventricular systolic dysfunction, prolonged QRS duration, myocardial fibrosis and pulmonary regurgitation [14].

Pathological mechanisms that result in cardiac arrhythmias include electrical instability due to formation of fibrosis and fat disposition at surgical scars as a consequence of TOF repair (i.e., re-entrant arrhythmias) [15]. In addition, residual structural heart defects may result in pressure and volume overloading, leading to potential atrial and ventricular remodeling. The current study confirmed previously published associations between diagnostic assessments and cardiac arrhythmias [5–7]. RV mass was an independent predictor of VT. In the general population, RV hypertrophy is associated with the development of heart failure, diastolic dysfunction, and cardiac death [16]. Myocardial stretching induced by volume overloading in combination with fibrosis development induced by pressure overloading might result in electrical instability leading to conduction disturbances. The current results are in line with Valente *et al.* in that RV hypertrophy is predictive of VT [7]. However, in contrast with our findings they concluded that RV dilation was not predictive of VT. Yet to date, CMR derived RV mass is not considered an important indication for possible therapeutic interventions like primary ICD implantation in most medical centers and in current guidelines [14]. We

showed that RV mass ≥ 50 g/m2 was the optimal cut-off value in predicting VT. Accordingly, we suggest that RV mass ≥ 50 g/m2 might be used as an additional prognostic marker in the follow-up of these patients. Intraventricular conduction delay and a right bundle branch block is a common electrocardiographic finding following TOF repair [17]. The current result that prolonged QRS duration is an important risk marker for VT is in line with previous studies [7, 10, 17]. Scar formation following surgical interventions and mechanical stretching of the RV may culminate the observed prolonged QRS duration in these patients. It has been shown that CMR derived RV dilatation is a key predictor of VT, SCD and impaired clinical status [18]. This is confirmed in the current study. RV systolic dysfunction proves to be a reliable risk marker for VT, which is in line with the findings of Bokma et al. and Knauth et al. [18, 19] Chronic hypoxia and pressure loading before TOF repair on the one hand, and chronic volume loading after repair on the other hand may lead to pathophysiological RV remodeling that is responsible for RV dysfunction, and concomitant cardiac tachyarrhythmia. In the present cohort, higher BMI was identified as a risk factor for VT. Obesity and its associated disorders are known to induce ventricular hypertrophy, fibrosis and increased epicardial fat [20]. These changes might form a substrate for electrical instability. In the general population, obesity also widely showed to be an independent risk factor for sudden cardiac death [21]. Furthermore, obesity is associated with subclinical RV dysfunction and increased RV volumes and wall thickness in the general population, and is often associated with other risk factors for arrhythmias (e.g. metabolic disease, hypertension, obstructive sleep apnea and diabetes mellitus) that may lead to remodeling and subsequently arrhythmia [22]. The observed association between higher BMI and increased risk of VT in our study could be regarded as in line with observations in the general population, added onto an already affected RV at risk of VT.

Supraventricular tachycardia is common and is an important cause of morbidity in patients with repaired TOF [5]. Patients experiencing atrial tachyarrhythmia are at risk for heart failure, re-intervention, VT, cerebral vascular accident and SCD [10, 15]. Higher BMI was the most important predictor of atrial tachyarrhythmia in the present cohort. In the general population, obesity is also considered a risk factor for atrial tachyarrhythmia [23]. Obesity is associated with atrial enlargement, ventricular diastolic dysfunction and pericardial fat deposition, and these are risk factors for developing atrial tachyarrhythmia. In addition, before-mentioned consequences of obesity contributive of risk of VT also increase the risk of atrial tachyarrhythmia. Our study was in line with previously published studies that have suggested older age at TOF repair is an independent predictor of atrial tachyarrhythmia [10, 17]. Several etiological factors have been described for this phenomenon, such as prolonged hemodynamic burden as a result of anatomic anomalies or the negative impact of palliative interventions. Increased duration of hemodynamic burden before correction surgery may induce increased atrial remodeling, such as increased atrial size and diffuse fibrosis, which may in turn lead to

subsequent atrial arrhythmia. Surgical interventions before correction, which may occur more often when correction age is higher, might lead to macro reentrant circuits localized around the atrial surgical scars [15]. The results provide additional evidence that early TOF repair might be beneficial in order to prevent the development of atrial conduction disturbances on the long-term. The results of this study may enhance the risk stratification of cardiac arrhythmias in patients with repaired TOF. Prospective longitudinal studies are required to determine if the suggested risk models contribute to more effective treatment strategies and better outcome in patients with repaired TOF.

This current analysis is limited by its retrospective nature. Only patients who underwent a CMR were included, which may have introduced a selection bias. Unfortunately, Doppler-based LV longitudinal strain, RV pressure data and atrial volumes, exercise data, diffuse myocardial fibrosis and use of late gadolinium enhancement assessed by CMR, were absent in this retrospective analysis. Because of the retrospective character of the study, the outcome parameters may have been missed in some patients, since Holter recordings were not made in all patients at standardized time points. In total, 18 TOF patients underwent a redo pulmonary valve replacement, which may be a confounder in the current analysis. No risk stratification for SCD was performed, since no SCD occurred in this study cohort.

CONCLUSION

Increased RV mass, RV end-systolic volume, and RV enddiastolic volume together with decreased RV ejection fractionon CMR, in addition to lengthened QRS duration are independent predictors of VT in patients with repaired TOF. The results suggest that in addition to RV dilatation and RV dysfunction, RV hypertrophy derived from CMR should be included in strategies and indications for primary ICD implantation. Older age at time of TOF repair was associated with the occurrence of atrial tachyarrhythmia. In addition, our study represents the only study thus far to describe the association between an high BMI with the occurrence of both atrial tachyarrhythmia and VT in Fallot patients. The present study therefore contributes to the risk stratification for cardiac tachyarrhythmia in patients with repaired TOF.

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