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Implications of atrial volumes in surgical corrected Tetralogy of Fallot on clinical adverse events☆

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ABSTRACT

Background: While left atrial (LA) size has been shown as a strong predictor of cardiovascular diseases in various studies, the role of right atrial (RA) enlargement, especially in the growing population of patients with congenital heart diseases (CHD) is largely unknown. We sought to evaluate (1) RA and LA volumes in patients with repaired Tetralogy of Fallot (TOF) and assess correlations to (2) functional parameters and (3) clinical adverse events.
Methods: 169 patients with repaired TOF were enrolled following a targeted protocol for Cardiovascular magnetic resonance imaging (CMR), Cardiopulmonary exercise tests (CPET), Echocardiography and Measurement of NT-proBNP. Clinical history was assessed at enrollment and during a median Follow-up of 23 months (IQR 9–40). The primary clinical endpoint was a composite of all cause mortality, aborted sudden cardiac death and sustained VT. Prespecified secondary surrogate endpoint included worsening heart failure (NYHA III–IV), non-sustained VT and sustained supraventricular tachycardia.
Results: RA Systolic indexed volume (RASVi) correlated with LA Systolic indexed volume (LASVi) ($r = 0.59$, $p < 0.001$) and both correlated with the patient age ($r = 0.52$, $p < 0.001$; $r = 0.59$, $p < 0.001$ respectively). Patients in the upper tertil of RASVi (>58 ml/m^2) had higher NT-proBNP levels, longer QRS duration, larger ventricle diameters, higher RV mass and lower peak oxygen uptake. RASVi was associated with the primary composite adverse event at univariate Cox-regression analysis (HR: 1.044, CI: 1.008–1.08, $p = 0.01$). Bayesian Multivariate model averaging revealed RASVi as predictor of secondary surrogate adverse outcome (HR: 1.06, CI: 1.053–1.068, Pb = 0,889).
Conclusion: Among patients with repaired TOF, RA dilatation is an independent predictor for adverse clinical events. As such, routine assessment of RA volumes could be useful to further improve decision-making and management of these patients in the future.

1. Introduction

LA enlargement has been shown as a reflection of clinical (or subclinical) cardiovascular disease [1–3]. As such, LA diameter is a strong predictor for mortality and cardiovascular events [2–6].

In contrast, there is only limited knowledge about the role of RA enlargement and its clinical implications, especially for primarily right sided pathologies in the growing population of congenital heart diseases (CHD).

Tetralogy of Fallot (TOF) and variants, being the most frequent cyanotic CHD, face clinicians with various challenges during long-term follow-up. In particular progressive RV dysfunction secondary to chronic RV pressure and/or volume overload is associated with arrhythmias, significant morbidity and mortality [7]. In the Absence of one single parameter, Guideline recommendations after initial successful surgical corrections are based on various surrogate parameters. Whether assessment of RA enlargement has similar predictive value for right ventricular (RV) function as the LA has for left ventricular function is uncertain.

The aims of the current study were to evaluate (1) RA and LA volumes in patients with repaired Tetralogy of Fallot (TOF) and assess correlations to (2) functional parameters and (3) clinical adverse events.

Abbreviations: LA, left atrium; RA, right atrium; CHD, congenital heart disease; CMR, Cardiovascular magnetic resonance imaging; RV, right ventricle; CPET, Cardiopulmonary exercise test; TOF, Tetralogy of Fallot; RASVi, right atrial endsystolic volume index; LASVi, left atrial endsystolic volume index; RVEDVi, right ventricular enddiastolic volume index; LVEDVi, left ventricular enddiastolic volume index.

☆ PS: We would like to precise that Dr. Giuseppe Rossi coauthor of this paper, our statistician who performed most of the statistical analysis of the study and a dear friend of us unfortunately passed away.

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2. Methods

2.1. Study population

From 2011 to November 2015, all patients aged >12 years with repaired TOF referred to our center were evaluated according to a standardized protocol including comprehensive clinical and surgical history, electrocardiogram (ECG), Cardiovascular magnetic resonance imaging (CMR), Cardiopulmonary exercise testing (CPET) and NT-pro BNP assay. Transthoracic echocardiography (TTE) was either performed during the initial visit, or extracted from existing medical reports to value the degree of tricuspid regurgitation and systolic RV pressure.

Exclusion criteria included contraindication for CMR; associated major cardiac anomalies as atrioventricular septal defects, major aorto-pulmonary collaterals, Ebstein anomaly and presence of pulmonary hypertension.

All patients or legal guardians gave their written informed consent when they underwent CMR.

2.2. Cardiovascular magnetic resonance imaging

CMR was performed using a Signa/GE CV/i 1.5T Signa Cvi scanner (GE, Milwaukee, Michigan, USA) and a surface four- and eight channel cardiac phased array coil. A comprehensive CMR evaluation was performed following an examination protocol for repaired TOF as previously described [8] In brief, both, LA and RA were covered extending the short axis ECG-triggered, steady-state free-procession (SSFP) stack up to the roof of the atria with a slice thickness of 7–8 mm, gap, 0, TR/TE equal to 3.5/1.5, 2; 30 phases, 10–25 views per segment depending on heart rate, NEX 1, FOV 34–36 cm, a matrix of 224 × 224, a 45° flip angle, and a bandwidth of 125 KHz. A commercially available gradient-echo velocity mapping ECG-triggered sequence (PVC-CMR) was used for the blood flow determination. Regurgitant fractions were calculated as percent backward flow over forward flow. Late gadolinium enhancement (LGE) was performed when clinically indicated [9].

Maximal RA and LA volumes were measured by manually tracing the endocardial border at end ventricular systole (Fig. 1). All volume measurements were indexed for body surface area. Inferior and superior vena cava and coronary sinus were excluded from RA analysis. Pulmonary veins were excluded from LA analysis.

According to RA-Volumes, the cohort was divided into tertiles. Group 1 (n: 59): RASVi ≤45 ml/m^2; Group 2 (n: 54): RASVi >45 ml/m^2 ≤ 58 ml/m^2; Group 3 (n: 56): RASVi > 58 ml/m^2.

2.3. Cardiopulmonary exercise test

Cardiopulmonary exercise test was performed in 150 patients using a bicycle ergometer. Work rate was increased according to a predefined ramp protocol with increments of 10–20 W/min in order to keep exercise duration between 8 and 12 min. Oxygen consumption (VO_2), carbon dioxide production (VCO2), and minute ventilation were measured using a breath-to-breath gas analysis (Vmax, SensorMedics, Yorba Linda, CA, USA). Peak VO_2 (the highest value at end-exercise, as a 20 second average) and ventilatory efficiency on exercise (ventilation slope vs VCO2 relation in its linear part) were determined.

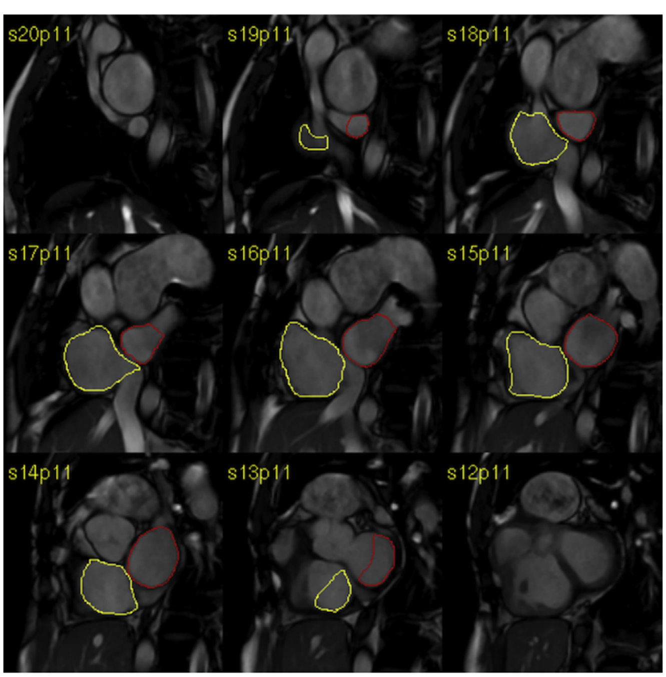

Fig. 1. Representative image of atrial volumes in short axis. A) Reference image: the stacks were extended to the roof of the atrii measurements of atrial volumes in short axis SSFP sequences. In red the left atrium, in yellow the right atrium.

2.4. Nt-proBNP

Blood samples were drawn from an antecubital vein after 20-min supine rest. NT-proBNP was measured by a fully automated electrochemiluminescence 'sandwich' immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD or median (25th; 75th percentiles) and categorical variables were expressed as frequency and percentage.

The correlation between continuous variables was investigated by the Pearson's correlation coefficient (r) and adjusted for age by the partial correlation. The comparison between groups for continuous variables was performed by analysis of variance (ANOVA) and by analysis of covariance (ANCOVA) adjusting for age. Unadjusted associations were assessed using a Chi square test. In order to evaluate the interobserver variability an interclass correlation was performed.

Follow-up data were obtained from at least one of the following sources: review of the patient's hospital record, personal communication with the patient's physician and review of the patient's chart, telephone interview, or patient visits to staff physicians at regular intervals in the out-patient clinic. The composite primary end point included all cause mortality, aborted sudden cardiac death or sustained VT. The composite secondary endpoint included worsening heart failure class (New York Heart Association III or IV), non-sustained VT or sustained supraventricular tachycardia (ectopic atrial tachycardia, atrial flutter or atrial fibrillation) [10].

In order to study the impact of the single covariate on primary and secondary endpoint, univariate Cox regression models were built (NTproBNP previously underwent a logarithmic transformation). The covariates found significant at the univariate analysis ($p < 0.05$) were considered for subsequent multivariate analysis. Considering the small number of events, to properly account for the uncertainty of models, a Bayesian average of Cox regression models was performed [11], producing a posterior probability for each possible model and each covariate. The P_b (posterior probability of being not null) of each covariate was used to establish the evidence of its effect: a $P_b \geq 0.99$ indicates a very strong evidence; a P_b in the range 0.95–0.99 stays for a strong evidence; a P_b in the range 0.75–0.95 stays for a positive evidence; P_b in the range 0.50–0.75 stays for a weak evidence. Bayesian model averaging analysis was performed with BMA package of the R statistical software [12].

Event-free survival curves were estimated using the Kaplan-Meier method. The comparison between RA volumes groups were investigated using the log-rank test.

All statistical tests with a 2-tailed $p < 0.05$ were considered statistically significant.

3. Results

3.1. Clinical and demographic data

Demographic, clinical and surgical data are summarized in Table 1. The study cohort consisted of 169 patients with repaired TOF (111 male; mean

Table 1
Study population: demographic and surgical characteristics.

Patients	N: 169
Tetralogy of Fallot	150 (89%)
DORV Fallot type[a]	6 (3.3%)
PA + VSD	13 (11.4%)
Male Sex	111 (66%)
Age (years)	28.1 ± 13 (12–70)
Previous shunt palliation	67 (39.6%)
Age at primary repair (years)	1.8 (0.84–4.2)
Type of primary RVOT repair	
TAP	106 (64%)
Infundibular patch/commissurotomy	51 (31%)
Valved conduit/homograft	9 (5%)
Unknown	4 (2%)
Type of RVOT at study	
TAP	81 (48%)
Native pulmonary valve	43 (25.5%)
Prosthetic valve/conduit/homograft	43 (25%)
Unknown	2 (1%)
Follow-up from correction (years)	24 ± 9.4

Legend: DORV: double outlet right ventricle; PA: pulmonary atresia; RVOT: right ventricular outflow tract; TAP: trans-annular patch; VSD: ventricular septal defect.

[a] In our study population none of patients with the diagnosis DORV presented a left ventricle outflow tract obstruction.

age 28.1 ± 13 years, range 12–70). Median age at primary surgical repair was 1.8 years (0.84; 4.2); mean follow-up time at study entry from primary repair was 24 ± 9.4 years. Forty-one patients (24%) have been re-operated for RV outflow tract dysfunction and underwent pulmonary valve replacement before the CMR study. Thirty-seven patients experienced an adverse event before the study, mainly atrial arrhythmias in 24 patients. In 5 patients a sustained ventricular tachycardia was reported, associated to atrial arrhythmias in 2 of them, while 6 patients presented a non-sustained ventricular tachycardia and 2 patients experienced heart failure and atrial arrhythmias.

3.2. Comparison between RA volume groups

Across the whole study population, mean RASVi was 54 ± 19 ml/m^2 and LASVi 31.5 ± 13 ml/m^2. According to RA-Volumes, the cohort was divided into tertiles. Group 1 (n: 59): RASVI ≤45 ml/m^2; Group 2 (n: 54): >45 ml/m^2 ≤ 58 ml/m^2; Group 3 (n: 56): >58 ml/m^2. Patients in the highest tertile were significantly older at time of primary repair and time of study entry. They had higher NT-proBNP levels, longer QRS duration, more dilated ventricles, higher RV mass, higher RV LGE, and lower VO_2/kg/min compared to the other 2 groups (Table 2). The interobserver variability of right and left atrial volumes with intraclass correlation was ICC = 0.7826, $p < 0.001$.

3.3. Factors associated to higher atrial volumes

RASVi correlated with LASVi ($r = 0.6$, $p < 0.001$) and both correlated with age at CMR imaging ($r = 0.52$, $p < 0.001$; $r = 0.59$, $p < 0.001$ respectively) and age at primary repair ($r = 0.49$, $p < 0.001$; $r = 0.7$, $p < 0.001$ respectively). Adjusting for age, the correlation between age at primary repair and RASVi and LASVi remained significant especially for LASVi (partial $r = 0.19$, $p = 0.014$; partial $r = 0.51$, $p < 0.001$ respectively).

RASVi positively correlated with end-diastolic indexed RV volumes (RVEDVi) ($r = 0.45$, $p < 0.001$) and end-diastolic indexed LV volumes (LVEDVi) ($r = 0.33$, $p < 0.001$), QRS length ($r = 0.36$, $p < 0.001$). RASVi was inversely related to RVEF and LVEF (respectively, $r = -0.22$, $p < 0.001$, $r = -0.23$, $p < 0.001$). LASVi correlated only with LVEDVi and LVESVi.

RASVi was larger in patients with moderate or severe tricuspid regurgitation compared to absent or trivial tricuspid regurgitation (63 ± 19.8 ml/m^2 vs. 51 ± 16.4 ml/m^2, $p < 0.001$).

During the follow-up period, a total of 38 patients underwent re-operation for pulmonary valve implantation or RVOT conduit substitution. Correspondingly follow up time was censored at time of re-operation or with occurrence of clinical adverse events.

During a median follow-up time of 23 months (IQR 9–40); 7 patients experienced a primary adverse event. 1 patient died for non-cardiac disease (cancer) and 6 patients experienced symptomatic ventricular tachycardia. Intracardiac defibrillator (ICD) was implanted in 3 cases, 2 patients underwent a transcatheter ablation and 1 patient underwent pulmonary valve implantation.

The secondary endpoint was met in 18 patients. 7 patients experienced right atrial flutter, 5 of them underwent a transcatheter ablation; in 1 patient atrial fibrillation was diagnosed confirmed by electrophysiological study while in1 patient both atrial fibrillation and right atrial flutter were diagnosed. In 3 others patient a run of right atrial tachycardia was diagnosed; 3 patients presented heart failure and a non-sustained ventricular tachycardia was reported in 3 patients.

At univariate regression Cox analysis (Suppl Table 1), the primary outcome was associated to age, NYHA class II/III, QRS, LASVi, RASVi, RVESVi and RVEF, TA patch at study; due to the small number of the primary events no multivariate analysis was performed.

Table 2
Characteristics of RASVi Groups.

	Total	Group 1[a] (n: 59)	Group 2[a] (n: 54)	Group 3[a] (N: 56)	p-value
Gender (male)	111 (66%)	36 (61%)	34 (63%)	41 (73%)	0.34
Age at study	28 ± 4.2	21.5 ± 9.4	26.4 ± 10.5	36.4 ± 14	<0.001
Previous shunt palliation	67 (40%)	18 (31%)	25 (46%)	24 (43%)	0.39
Age at primary repair (years)	1.8 (0.84; 4.29)	0.98 (0.69; 2)	2.1 (0.87; 3.7)	3.8 (1.45; 8.9)	<0.001
Type of primary RVOT					0.42
Infundibular patch	51 (31%)	14 (25%)	16 (31%)	21 (41%)	
TAP	105 (64%)	41 (72%)	34 (63%)	30 (56%)	
Valved conduit/homograft	9 (5.5%)	2 (3.5%)	4 (7.5%)	3 (5.6%)	
Type of RVOT at study					0.59
Native pulmonary valve	43 (25.4%)	12 (20%)	13 (24%)	18 (32%)	
TA patch	81 (48%)	31 (53%)	25 (46%)	25 (45%)	
Prosthetic valve	43 (25%)	15 (25%)	16 (30%)	12 (21%)	
NYHA II/III vs I	24 (14%)	6 (10%)	5 (9%)	14(24%)	0.06
Ln NtProBnp	4.7 ± 0.97	4.26 ± 0.69	4.59 ± 0.92	5.2 ± 1	p < 0.001
VO_2/kg/min	25.9 ± 7.4	26.4 ± 6.7	27.5 ± 8.1	23.8 ± 7	0.03
Watt	118 ± 36	107 ± 31	126 ± 33	122 ± 39	0.015
QRS (msec)	151 ± 27	142.0 ± 23.8	151 ± 25	164 ± 27.5	p < 0.001
LASVi (ml/m^2)	31.5 ± 13	25.4 ± 6.5	30 ± 7.7	39.5 ± 17.6	p < 0.001
LVEDVi (ml/m^2)	86.4 ± 17	81 ± 16	85.7 ± 17	92.6 ± 16.5	p = 0.001
LVEF (%)	58.6 ± 6.5	59.6 ± 5.2	59 ± 7.4	56.8 ± 6.7	p = 0.06
RVEDVi (ml/m^2)	142 ± 38	123 ± 29	137 ± 36	165.5 ± 35.7	p < 0.001
RVEF (%)	50 ± 8.1	51.8 ± 6	50.5 ± 8.1	48 ± 9.5	p < 0.001
RV mass (g/m^2)	37 ± 11	32.3 ± 10	38 ± 12	40.4 ± 9.5	p < 0.001
Right LGE	4.68 ± 1.7	4.02 ± 1.66	4.57 ± 1.85	5.5 ± 1.4	p < 0.001
PRF (%)	27 ± 18.5	23.6 ± 18.7	25.8 ± 18.6	31.9 ± 17.6	0.049
SBP	112 ± 21	106 ± 16.6	110 ± 12.7	112 ± 21	0.19
RVP (mm Hg)	48 ± 19.6	46.4 ± 19	50.7 ± 21.1	47.8 ± 18.9	0.586
Significant tricuspid regurgitation	35 (21%)	5 (8.5%)	12 (23%)	18 (34%)	0.004
Re-operated patients °(%)	41 (24%)	14 (24%)	15 (28%)	12 (21%)	0.73
Previous cardiac event	37 (22%)	6 (10%)	7 (14%)	24 (43%)	<0.001

Legend: LASVi: left atrium indexed systolic volume; LGE: late gadolinium enhancement; LVEF: left ventricle ejection fraction; LVEDVi: left ventricle end-diastolic volume; LVESVi: left ventricle end-systolic volume; PRF: pulmonary regurgitation fraction; RASVi: right atrium indexed systolic volume; RVEF: right ventricle ejection fraction; RVEDVi: right ventricle end-diastolic volume; RVESVi: right ventricle end-systolic volume; RVP: right ventricle pressure; SBP: systolic blood pressure; TAP: trans-annular patch; TR: tricuspid regurgitation.

[a] Group 1 (n: 59): RASVI ≤45 ml/m^2; Group 2 (n:54): >45 ml/m^2; ≤58 ml/m^2; Group 3 (n: 56): >58 ml/m^2.

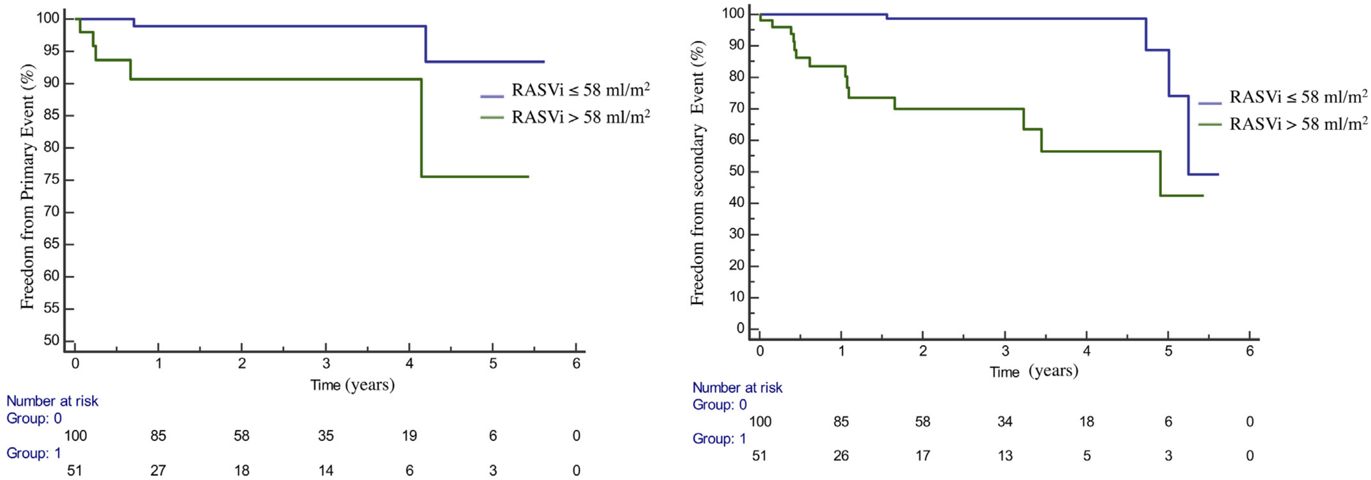

Fig. 2. Kaplan-Meier survival curve showing patients with RASVi>58 ml/m^2 had a significantly increased risk of primary outcome (log-rank test, $p = 0.01$) and secondary outcome at follow-up. RASVi: right atrium systolic volume indexed.

The following covariates were associated with the second endpoint (Suppl Table 2): age, age at primary repair; ln NT-ProBNP, VO_2/kg/min, QRS length, LASVi; RASVi; RVEDVi; RVESVi; RVEF; right LGE.

The multiple Bayesian model averaging analysis identified age (HR: 1.26, CI: 1.24–1.29, Pb = 1), age at primary repair (HR: 1.11 CI: 10–1.29, Pb = 0.95 and RAVSi (HR: 1.06, CI: 1.053–1.068, Pb = 0.889) as significant predictors of secondary outcome (Suppl Table 3).

No association was found between the subgroup of pulmonary atresia with ventricular septal defect (PA-VSD) and the observed events ($p = 1.000$ for primary outcome; $p = 0.979$ for secondary outcome).

In the group of patients with RASVi > 58 ml/m^2 (upper tertil) the primary outcome occurred more frequently (Chi square: 4.9; $p = 0.02$) as well as the secondary outcome (Chi square: 18.5; $p < 0.001$) compared to the remaining population. There were also more frequent re-interventions in the upper tertil (Chi square: 19.6; $p < 0.001$).

By Kaplan-Meier survival analysis (Fig. 2), patients with RASVi> 58 ml/m^2 had a significantly increased risk of primary outcome (log-rank test, $p = 0.01$) and secondary outcome at follow-up (log-rank test, $p < 0.001$).

4. Discussion

To the best of our knowledge, this is one of the largest study evaluating the relationship of atrial volumes and outcome in patients with repaired TOF patients.

The key findings of our study are: 1) RA dilation is associated with common parameters of RV dysfunction; 2) RASVi is an independent factor for adverse cardiac events at follow-up; 3) a strong correlation was found between right and left atrial volumes.

Several studies evaluated LA dimensions and their clinical significance in left heart diseases [1,2,4–6]. Although RA measurement has not been introduced into routine clinical practice, there is some evidence of its prognostic value in chronic heart failure [13], atrial fibrillation [14] and pulmonary arterial hypertension [15]. Recent work also showed abnormal RA performance in repaired TOF [16].

One reason for it's limited distribution in clinical routine up to date, might be due to the technical difficulty to assess right atrial dimensions and volumes. In current practice, atrial dimensions are mainly based on diameters or area curves [17], despite the increasing evidence that left atrial volumes are superior to diameters for the accurate measurement of the atrial size [17,18]. As an increasing number of patients in the post-operative follow-up of TOF undergo CMR, RA volumes can be obtained with relative ease. Practically, the quantification of atrial volumes can be achieved by simply extending the ventricular short axis stack up to atrial levels.

As expected, RA volumes correlate with age and RA dilation is linked to the degree of tricuspid regurgitation.

According to our data, dilatation of the RA was associated to common prognostic factors in repaired TOF: patients in the highest tertile of RASVi had higher NT-proBNP levels, an already validated biomarker in this population [19,20]. RASVi and LASVi correlate with age at primary repair, a well recognized prognostic factor in post repaired TOF [7]. Importantly, RA volumes predicted clinical outcome independently from age, raising the question of whether RA dilatation purely indicates more advance disease or whether this parameter represents a distinct pathological entity in post-operative TOF patients. It is well known that chronic adverse RV loading conditions will increase filling pressures and thereby also RA pressures, which in term will lead to RA dilatation [21]. The strong association between RA volumes and common parameters of RV dysfunction supports the concept of RA dilatation as a marker for underlying ventricular pathology. However, studies on left atrial function demonstrated that increased atrial pressures and chronic fibre stretch results in structural remodeling and atrial fibrosis, which in turn causes electrical remodeling [7,21] and a substrate for atrial arrhythmias. In keeping with previous reports [21,22–25], atrial arrhythmias were common in our cohort and contributed to adverse events. Atrial arrhythmias are often not tolerated in these patients leading to hospitalization and congestive heart failure [26]. As such, it seems reasonable to assume that RA dilatation resulting in increased risk for atrial arrhythmia contribute independently to adverse events in repaired TOF.

Finally, the correlation between RA and LA volumes mirroring the well established interaction between the LV and RV [27–29] in this population.

Irrespective whether RA dilatation represents an independent disease entity or just a surrogate for more advanced underlying RV disease, the occurrence of atrial tachyarrhythmias predicts death and sustained VT in adults with repaired TOF [7]. Therefore, we propose to include routine assessment of RA volumes in the diagnostic work up of these patients. Further studies are needed to understand how to integrate these parameters in the process of clinical decisions in the management of this challenging group of patients.

The study was performed at tertiary referral centers for CMR in adult congenital heart disease. Therefore, we cannot exclude the possibility of a selection bias. However in the current era, all patients without a contraindication underwent CMR in a routine follow-up. Moreover we have no data on RV diastolic function in our patients to link to RA volumes. Furthermore because of the sample size and limited follow-up period no multivariate analysis was performed for this endpoint. Larger longitudinal studies are warranted to better investigate the impact of atrial dilatation on primary outcome and confirm our results.

In conclusion in repaired Tetralogy of Fallot, RA dilatation is an independent predictor for adverse clinical events. As such, routine assessment of RA volumes could be useful in diagnostic workup to further improve the management of these patients in the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.018.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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