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Long-term assessment of clinical outcomes and disease progression in patients with corrected Tetralogy of Fallot

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Abstract. – OBJECTIVE: Understanding changes of right ventricular (RV) geometry and function in repaired Tetralogy of Fallot (rToF) patients can improve decision-making for pulmonary valve replacement. Therefore, we aimed to assess the magnitude and clinical correlations of RV changes in rToF patients.

PATIENTS AND METHODS: Clinical and MRI data of rToF patients who underwent repeated cardiac magnetic resonance imaging (MRI) at two centers between December 2003 and September 2020 were analyzed together with anatomical factors, including RV outflow tract obstruction, pulmonary artery branch stenosis, and tricuspid regurgitation. Adverse cardiac events and/or NYHA class worsening were documented and correlated with MRI changes. QRS length was reported at each MRI.

RESULTS: Two-hundred-and-nineteen rToF patients (53% males, aged 20.2 ± 10.1 years) were enrolled. An increase of ventricular dimensions, except LVEDVi, and worsening of right and left ejection fractions were found over an average period of 5 years of follow-up. These changes were statistically significant but within 10% of the initial value. No significant changes were reported on a year-to-year basis, except in a small group of patients (6%) in whom no predictive factors were identified. Despite similar RV dimensions at the first examination, younger patients had a higher RV ejection fraction and a different annual rate of change of ventricular dimensions compared to older ones. Patients with arrhythmias (20%) were more frequently older and had larger RV dimensions but showed no significant correlations with MRI changes/years.

CONCLUSIONS: Changes in RV dimensions and function occur rarely and very slowly in rToF patients. A small percentage of patients experience a significant worsening in a short time interval without any recognized risk factors. Arrhythmias appear to occur in a small percentage of cases in the late follow-up.

Key Words:
Tetralogy of Fallot, Cardiac magnetic resonance, Right ventricle, Repaired tetralogy of Fallot.

Introduction

Tetralogy of Fallot repair (rToF) leads to chronic pulmonary valve regurgitation, which causes right ventricular (RV) volume overload with consequent dilation[1]. This has a harmful effect on RV function, with ultimate functional impairment[2,3]. The onset of myocardial dysfunction is due to a combination of multiple factors, whose involvement varies from patient to patient over time and is still difficult to predict based on current knowledge. Accurate prediction

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of the threshold value of RV dilation beyond which dysfunction arises would be fundamental, given that RV function impairment appears to be irreversible and non-modifiable by pulmonary valve replacement (PVR)[4,5].

Cardiac magnetic resonance imaging (MRI) is the gold standard for the assessment of the RV and the indication for PVR in asymptomatic patients is mainly based on MRI parameters[6,7]. Cut-off values for RV end-diastolic volume indexed (RVEDVi) to body surface area (BSA) between 150 and 170 ml/m^2 have been proposed as an indication for PVR in asymptomatic adults with rToF[7]. However, the rate of progression of RV dilation is highly variable among different subsets of rToF patients. Several previously published studies[8-10] have tried to single out the factors (age at repair, era of repair, type of repair, presence of a systemic-to-pulmonary shunt for palliation before complete surgical repair, degree of pulmonary regurgitation, residual RV outflow tract obstruction, pulmonary branches stenosis) involved in the progression of RV dilation. However, to date, the literature provides no clear insight into the incidence of each factor involved in RV dilation over time. Moreover, there is no unanimous consensus about the timing of the first MRI and its frequency in rToF patients before they undergo PVR.

The aim of our study was to assess longitudinal RV changes to better understand the mechanisms involved in RV dilation and dysfunction over time in rToF patients with transannular (TP) and/or infundibular (IP) patch, and to correlate these changes with the onset of adverse cardiac events. In addition, we sought to evaluate whether the progression of MRI parameters in patients with RVEDVi≥ 150 ml/m^2 at the first MRI was different from those with a smaller RV size.

Patients and Methods

Patient Population

The patient logs of MRI laboratories at Bambino Gesù Children's Hospital in Rome and at Heart Hospital FTGM in Massa-Pisa were searched for all rToF patients who underwent more than one MRI study between December 2003 and September 2020. The timing of the first MRI was discussed for each patient at the hospital's multidisciplinary meetings and based on clinical assessment and qualitative echocardiographic evaluation. The timing of the following MRIs was based on the evaluation of RV size at the first exam (2-3 years for moderate dilation, 1 year for severe dilation) and on the clinical condition of patients, according to clinical guidelines[11]. Patients with RV-to-pulmonary artery conduits, additional structural lesions (e.g., common atrioventricular canal or heterotaxy syndrome), or previous PVR were excluded. Moreover, children under 10 years old were also excluded as MRI is often performed under general anesthesia in this population given the lack of cooperation[11]. The following data were collected: clinical and surgical history, NYHA class, QRS length at ECG. Cardiac events during follow-up were also documented, including aborted sudden cardiac death and all causes of death, sustained (longer than 30 seconds) and non-sustained ventricular tachycardia (VT/NSVT), sustained supra-ventricular tachycardia (ectopic atrial tachycardia, atrial flutter, or atrial fibrillation) and pacemaker or ICD implant. When the patient performed PVR, his/her follow-up was censored at the time of PVR. The study was approved by the Ethics Committee of Bambino Gesù Children's Hospital IRCCS (Prot. number 67080).

MRI Imaging

MRI examinations were performed with on 1.5 T scanners (in one center up to 2014 on an Achieva scanner, Philips Medical, Best, The Netherlands until 2014 and on an Avanto scanner, Siemens, Erlangen, Germany afterwards; in the other center on a Signa CV/i, GE Medical Systems, Milwaukee WI, USA). The study protocol for repaired TOF was performed as previously described, including cine steady-state free precession sequences for volume and function assessment and phase-contrast imaging for flow assessment at the tricuspid, pulmonary, and aortic valves, and at both pulmonary branches, as previously reported[12,13].

Image Analysis

The acquired data were analyzed offline on a separate workstation using cardiac post-processing software (Viewform, Philips Medical, Best, The Netherlands or Mass plus Version 4 and FLOW Version 4, MEDIS, Medical Imaging Systems, Leiden, The Netherlands). Assessment of left ventricular (LV) and RV volumes was performed by manual segmentation of short-axis cine images at end-diastole and end-systole and calculated using the method of discs. Papillary muscles were included in the blood pool. Stroke volume (SV) and ejection fraction (EF) were calculated from the measured volumes. Blood flow was calculated from phase-contrast images using a semiautomatic edge-detection algorithm with operator correction. The regurgitant fraction was calculated as the retrograde flow divided by the forward flow.

In addition, the following data were considered on echocardiography: 1) flow velocity across the RV outflow tract (RVOT) or a branch pulmonary artery ≥ 3 m/sec; 2) systolic RV pressure derived from tricuspid regurgitation ≥ 45 mmHg. In each center, there was only one observer who analyzed all the exams. Interobserver and cross-center comparisons of MRI quantification were not higher than 10% for volumes and ejection fractions of both ventricles, as reported in previous papers[14-16].

Right ventricular end-diastolic volume indexed to BSA (RVEDVi) change per year was calculated as follows: the number resulting from the difference between RVEDVi at the last and RVEDVi at first MRI was normalized per year. Similarly, right ventricular ejection fraction (RVEF) change per year, LVEDVi change per year, and LVEF change per year were obtained.

Right ventricular and LV volumes and function were considered unchanged if the variability of the measurements between two studies was within 10%, representing a non-significant interstudy variation, as reported in previous works[14-16]. Patients with more than 10% of RVEDVi change were compared with the remaining population. Moreover, the population study was subsequently divided into subgroups according to age (adult patients *vs.* pediatric patients), gender, RVEDVi at the first MRI (> 150 ml/m^2 and < 150 ml/m^2)

Statistical Analysis

When appropriate, data were expressed as mean ± standard deviation or median and interquartile range (IQR 25°-75°). Differences between groups were tested for statistical significance using Student's *t*-test or Mann- Whitney or Kruskal-Wallis test for continuous variables when appropriate. The chi-square test was used for categorical variables. In the case of repeated measures for continuous variables, paired samples *t*-test or Wilcoxon signed-rank test were used when appropriate. The correlation between continuous variables was tested with Pearson's correlation r coefficient or Spearman when indicated. All statistical tests with a 2-tailed $p<0.05$ were considered statistically significant. All analyses were performed using SPSS. (Armonk, NY, USA; version 21.0).

Results

Study Cohort Characteristics

Two hundred and nineteen rToF patients (53% male) were included in the study. The mean age was 20.2 ± 10.1 (range 10.0-54.6) at the time of enrollment and 25.1 ± 10.4 years (range 12 – 62) at the time of the last MRI. Most patients underwent a TP repair (83.1%), with 58 patients (26.5%) undergoing a Blalock Taussig shunt before definitive repair. The median age at the time of repair was 12.7 months. In 157 (72%) patients, more than 2 MRIs were performed. The mean time interval between the first and the last examination was 4.8 ± 2.4 years.

Ventricular Parameters in the Overall Observed Period

At a median follow-up of 4.5 years, a statistically significant increase of RV and LV dimensions with a worsening of both right and left EFs was observed in all patients, without changes in the pulmonary regurgitation fraction (PRF) (Table I). Ventricular size and function modifications were within 10% of the initial value. No significant annual changes were observed for MRI parameters in almost the entire population (94%). Only 13 patients (6%) had a > 10%/year increase in RVEDVi (Table II), with a trend to a larger LV and a more significant tricuspid regurgitation (TR) (Table II). Adverse clinical events were not different between the two groups (with or without significant annual MRI parameters change) (Table II).

Correlations Between MRI Parameters Changes and Patients' History

Right ventricular ejection fraction change/year correlated negatively with baseline RVEF, with LVEF change /year (respectively R=-0.25; $p<0.001$; R=0.42; $p<0.01$) and with age at surgery (R=-0.2; $p=0.02$). RVEDVi change/year was linked with LVEDV change/year (R=0.6; $p<0.01$) and with baseline LVEDVI and LVESVI (R: -0.23 $p<0.001$). In addition, RVEDVi correlated negatively with the patient's age (R=-0.23; $p<0.01$). Previous palliation surgery and/or the type of repair, as well as the presence of RVOT or pulmonary artery branch stenosis, had no impact on the rate of RVEDVi and RVEF change/year. Left ventricular end-diastolic volume indexed to BSA change/year correlated negatively with LVEDVi at the first MRI (R=-0.34; $p<0.01$), with patient age (R=-0.12; $p=0.01$) and with age at surgery (R=-0.2; $p=0.01$).

Comparison Between Patients with RVEDVi ≥ 150 ml/m² and < 150 ml/m²

Forty-nine patients (22%) had an RVEDVi > 150 ml/m^2 at the first MRI exam and were compared with the 170 patients who presented with an

RVEDVi < 150 ml/m^2 at their first MRI scan (Table III). Annual changes in ventricular volumes and function were not different between the two groups. Only the PRF annual change was slightly higher in patients with a larger RV (Table III). Patients with RVEDVi ≥ 150 ml/m^2 were older at repair, had significantly longer QRS and lower RVEF values, without any difference in terms of LVEF (Table III). In addition, they had greater PRF and TR at both MRI exams. Finally, they had adverse cardiac events more frequently during follow-up (Table III).

Comparison Between Children and Adults

Ninety-seven patients (44%) were older than 18 years, at enrollment, with a median age of 23 years. The median age of those younger than 18 was 12.5 years. The younger population was operated earlier (p<0.001), rarely needed shunt palliation (12.4% vs 44.8 %, p<0.01) and more often underwent a TP (87.6% vs 75.6%, p=0.02). At baseline evaluation, this group showed a higher RVEF but similar RVEDVi compared to older patients (Table IV).

During a similar time interval, the annual rate of change of RVEDVi, LVEDVi, LVESVi, and PRF was significantly different in the younger population without functional impairment (Table IV; Figure 1). Cardiac events were significantly higher in older patients.

Comparison Between Genders

Higher values of RV dimensions and LVEDVi without significant differences in EFs were found in males at the first MRI. The annual changes of MRI ventricular volumes were not statistically significant in either group (Table V). Only the annual RVEF change was slightly higher in the males. Males were as likely as females to have adverse cardiac events.

Clinical Follow-Up

During a median follow-up of 7.3 (IQ 4.5; 9.7) years from the first MRI and 24 (IQ 18-32) years from the repair, 45 patients (20.5%; mean age at event 37.6 ± 11.6 years) experienced an adverse cardiac event: 24 of them had significant atrial arrhythmias; 2 had a worsening of NYHA class; 3 had symptomatic sustained ventricular tachycardia and 16 had asymptomatic no sustained ventricular arrhythmias at Holter. Moreover, 58 patients underwent PVR, and their follow-up was ended at this time. There was no association between ventricular volumes and function change/year and adverse cardiac events at follow-up in the overall population.

Discussion

Our study, carried out in a homogeneous group of pediatric and adult rToF patients, documented the absence of significant annual changes of MRI parameters in almost the entirety of our population (94%), also in the presence of a significant RV dilation. In addition, we did not find any associations between adverse cardiac events and ventricular volumetric and functional change over time. However, our data also showed a higher incidence of adverse cardiac events in patients with significant ventricular dilation and/or older age, supporting the hypothesis that significant hemodynamic alteration caused by chronic pulmonary incompetence tends to alter the electrical stability of rToF patients in the long-term[17].

Table I. Ventricular parameters over time. Legend: BSA: Body Surface Area, RVEDVi=right ventricle end-diastolic volume indexed to BSA; RVESVi=right ventricle end-systolic volume indexed to BSA; RVEF=right ventricle ejection fraction, LVEDVi=left ventricle end-diastolic volume indexed to BSA; LVESVi=left ventricle end-systolic volume indexed to BSA; LVEF=left ventricle ejection fraction; PRF=pulmonary regurgitation fraction.

Parameters	First MRI	Last MRI	*p*-value	% change	% change/year
Age (years)	20.3 ± 10	25.1 ± 10.4	<0.01	-----	-----
BSA	1.56 ± 0.26	1.69 ± 0.26	<0.01	-----	-----
RVEDVi (ml/m^2)	132 ± 33	141 ± 3	<0.01	4.3 (IQ:-2.6;14.9)	0.88(IQ:-0.7;3.1)
RVESVi (ml/m^2)	60 ± 20	67 ± 22.0	<0.01	8.62(IQ:-1.6.23)	1.83 (IQ:-0.4;5.3)
RVEF (%)	55.3 ± 6.5	53.1 ± 6.0	<0.01	-3.4 (IQ:-8;9.1.9)	-0.82 (IQ :-2.-0.82)
LVEDVi (ml/m^2)	78.6 ± 12.6	79.7 ± 14.0	0.37	0.97 (IQ:-7.5;10.6)	0.11 (IQ:-1.6;2.4)
LVESVi (ml/m^2)	31 ± 7.6	34 ± 8.7	<0.01	5.8 (IQ:-8.2;24)	1.3 (IQ:-2;5.6)
LVEF (%)	60.6 ± 5.6	58.4 ± 5.6	<0.01	-3.4 (IQ:-8.8;.1.9)	-0.7 (IQ:-2.3;0.5)
PRF (%)	35.8 ± 14	36.3 ± 14	0.19	0 (IQ:-7;10)	0 (IQ:-1.6;2.2)

Table II. Comparison between patients with change/year <=10% and >10% at the first MRI. Legend: BSA=Body Surface Area; TP=transannular patch; RVEDVi=right ventricle end-diastolic volume indexed to BSA; RVESVi=right ventricle end-systolic volume indexed to BSA; RVEF=right ventricle ejection fraction; LVEDVi=left ventricle end-diastolic volume indexed to BSA; LVESVi=left ventricle end-systolic volume indexed to BSA; LVEF=left ventricle ejection fraction; RVP=right ventricle pressure; Tricuspid regurgitation at the first*=Tricuspid regurgitation more than moderate at the first MRI; PRF=pulmonary regurgitation fraction.

Parameters	RVEDVi change/year ≤ 10% (n = 206)	RVEDVi change/year > 10% (n = 13)	*p*-value
Age (years)	16.1 (12.2-27)	13 (11.1-27)	0.3
BSA	1.58 (1.3-1.7)	1.6 (1.3-1.8)	0.54
Male (n;%)	109 (53)	7 (54)	0.9
Age at repair (months)	13 (6.7-31)	9.3 (7.2-41.4)	0.9
Previous shunt (n;%)	55 (27)	4 (23%)	0.75
TP (%)	171 (83)	11 (85)	0.8
NYHA II/III n (%)	12 (6)	2 (16.7)	0.1
QRS length (ms)	134 ± 26	148 ± 30	0.7
RVEDVi (ml/m^2)	132 ± 32	136 ± 46	0.9
RVEDVi ≥ 150 ml/m^2 (n%)	45 (21.8)	4(30.8)	0.4
RVESVi (ml/m^2)	59.5 ± 20	64.2 ± 24	0.4
RVEF (%)	55.3 ± 6.1	54 ± 5.2	0.4
LVEDVi (ml/m^2)	79 ± 12	72.1 ± 15	0.05
LVESVi (ml/m^2)	31.2 ± 7.5	28.7 ± 8.4	0.2
LVEF (%)	60.7 ± 5.6	60.5 ± 5.2	0.8
RVP (mmHg)	44 ± 13	45 ± 14	0.86
Tricuspid regurgitation at the first* MRI (%)	23 (11)	4 (31)	0.07
PRF (%)	35 ± 14	40 ± 16	0.38
Cardiac events at follow-up	42 (21)	3 (23.1)	0.83

A limited increase of RV dimensions with an almost imperceptible EF reduction was only shown in our rToF population over a median period of 5 years. However, even though the changes were significant from a statistical point of view, they were within the 10% of inter- and intra-observer variabilities reported in the literature[14-16]. Furthermore, also LV modifications, although statistically significant, were minimal, suggesting that major changes affecting both ventricles require time to happen. Such evidence supports the fact that it is not necessary to perform an MRI before 3 years have gone by in the majority of asymptomatic rToF patients, as indicated by clinical guidelines[8,11,18-21].

Our study highlighted that the changes in dimensions and function of both ventricles, even in patients with significant RV dilation ≥ 150 ml/m2 (33% of our cohort) – a value included among the criteria for PVR until recently[7] – occurs very slowly and rarely in a year. These data, in agreement with Luijnenburg et al[20], need to be confirmed on a wider number of patients but could bring about a more cautious approach in the indication of PVR in asymptomatic patients.

Only in 6% of patients, RV growth was > 10% in a year. Interestingly, this group did not show any significant difference in either MRI or clinical parameters compared to the other. In contrast, Wijesekera's study[18] found that rToF adults with a rapid progression rate of RV dimensions had larger RV volumes in addition to a lower RVEF at initial assessment. Based on our results and in agreement with the literature[19,22], by reporting no significant differences in surgical history, arrhythmias, echocardiographic and MRI baseline parameters between patients with and without rapid RV worsening, it is still difficult to understand which patients will have a more unfavorable course.

The negative correlation which emerged between RVEDVi and patient age (although weak) associated with different annual RV growth found when we subdivided our cohort in patients younger (median age of 13) and older than 18 (median age of 23) suggests that RV dilation could be constant even if minimal until a certain age, possibly corresponding to the completion of pubertal growth. Therefore, this different RV behavior could be nothing other than the "physiologic"

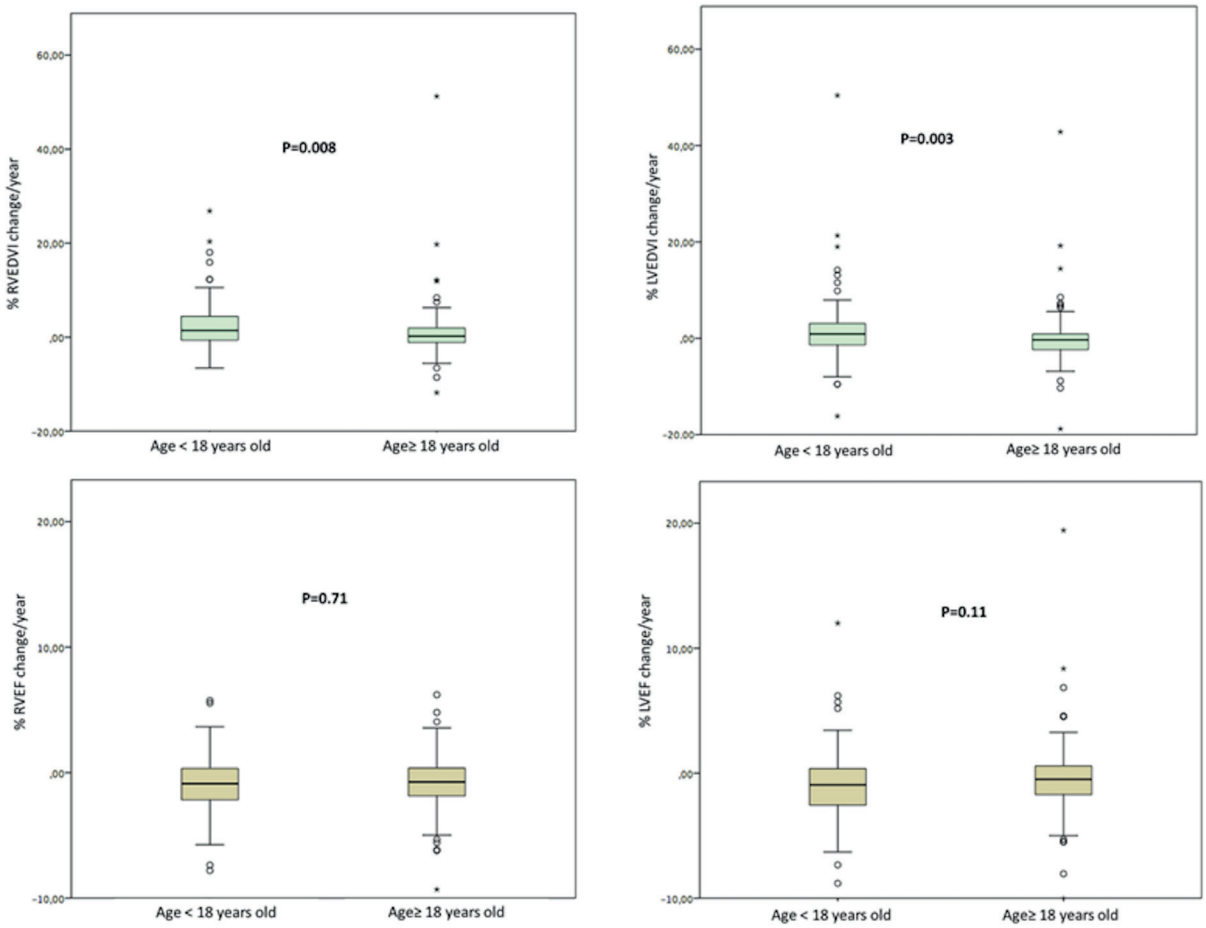

Figure 1. The figure shows the annual changes of RVEDVi (a), LVEDVi (b), RVEF (c), and LVEF (d) in patients younger and older than 18.

growth of cardiac chambers, existing in the age-range between 10 and 18, given that RV modifications in adolescents in our study do not seem clinically relevant, as reported by other authors[9,10]. However, the different RV growth over time in older patients could also be partially explained by the "Greutmann theory"[23], according to which RV remodeling occurs early after initial surgical repair and is followed by a "steady state" characterized by a dilated but stable RV. This theory could also explain why, despite similar RVEDVi values at the first MRI examination between patients younger and older than 18 years, we found a significantly worse RVEF in older patients. In fact, the persistence of a severe chronic pulmonary regurgitation over time may lead to the failure of compensatory mechanisms that preserve the RVEF, even if RV growth might come to a stop at a certain moment of the patient's life[23]. Surprisingly, another interesting fact that emerged from our results is that the patient's surgical history and hemodynamic alterations as RVOT stenosis and/or pulmonary artery branch stenosis do not seem to influence RVEDVi and/or RVEF changes/year. This seems to be contradicted by other studies[24-26]. However, we believe that RV modifications, which are almost close to zero in one year, should be evaluated over a longer period of time in order to reach the statistical significance of the above-mentioned correlations.

Atrial arrhythmias were the most frequent cardiac events at follow-up in our cohort, with a low incidence of sustained ventricular tachycardias. All adverse cardiac events were not significantly correlated to the annual change of MRI parameters but were more frequent in patients with significant RV dilation and in older subjects. The higher prevalence of arrhythmias in older patients is consistent with earlier studies that reported a relatively quiescent period 10 to 15 years after corrective surgery, followed by a steady decline in freedom from atrial and ventricular arrhythmias[27,28]. On

Table III. Comparison between patients with RVEDVi ≥ 150 ml/m² and the remaining patients. Legend: BSA = Body Surface Area; TP = transanular patch; RVEDVi = right ventricle end-diastolic volume indexed to BSA; RVESVi = right ventricle end-systolic volume indexed to BSA; RVEF = right ventricle ejection fraction; LVEDVi=left ventricle end-diastolic volume indexed to BSA; LVESVi = left ventricle end-systolic volume indexed to BSA; LVEF=left ventricle ejection fraction; RVP = right ventricle pressure; Tricuspid regurgitation* = more than moderate; PRF = pulmonary regurgitation fraction.

Parameters	RVEDVi ≤ 150 ml/m² (n=170)	RVEDVi > 150 ml/m² (n=49)	*p*-value
Age (years)	19.2 ± 9.2	23.7 ± 12	0.006
BSA	1.55 ± 0.26	1.6 ± 0.27	0.24
Male (n; %)	85 (50%)	31 (63.3%)	0.1
Age at repair (months)	11.5 (6.4-25.5)	19.8 (8.2; 48)	0.02
Previous shunt (%) n: 217	40 (24)	18 (36.7)	0.07
TP (%)	138 (81.2)	44 (89.8)	0.1
NYHA (II/III) n (%)	9 (5.5)	5 (10.2)	**0.2**
QRS (msec)	129 ± 24.4	153 ± 25	< 0.001
RVEDVi (ml/m²) at first MRI	118 ± 19.5	180 ± 23.6	<0.001
RVEDVi (ml/m²) at last MRI	128 ± 26	186 ± 29	**<0.001**
% RVEDVi change/year	0.95 (-04;3.2)	0.5(-1.2;2.6)	0.1
RVESVi (ml/m²) at first MRI	52 ± 11.8	88.3 ± 17.5	**<0.001**
RVESVi (ml/m²) at last MRI	58.7 ± 16	94.7 ± 22.7	**<0.001**
% RVESVi change/year	1.66 (-0.44.5.2)	1.98 (-0.48;5.8)	0.7
RVEF (%) at first MRI	56.3 ± 5.6	51.5 ± 5.8	**<0.001**
RVEF (%) at last MRI	54.4 ± 5.6	49.7 ± 5.8	**<0.001**
% RVEF change/year	-0.74 (-1.78; 0.39)	-1 (-3.5;0.19)	0.1
LVEDVi (ml/m²) at first MRI	77 ± 12.3	84.8 ± 11-3	**<0.001**
LVEDVi (ml/m²) at last MRI	78 ± 14	85.3 ± 13	**0.001**
% LVEDVi change/year	0.14 (-1.7; 2.4)	0 (-1.8;1.5)	0.6
LVESVi (ml/m²) at first MRI	30.2 ± 7	34 ± 8.8	0.02
LVESVi (ml/m²) at last MRI	33.6 ± 8.6	34.7 ± 9	0.4
% LVESVi change/year	1.42 (-1.5; 5.5)	0 (-3.3;5.8)	0.1
LVEF (%) at first MRI	60.5 ± 5.5	61.3 ± 6	0.38
LVEF (%) at last MRI	58 ± 5.2	59.6 ± 6.5	0.07
% LVEF change/year	-0.74 (-1.95; 0.52)	-0.56 (-3;0.59)	0.68
RVP (mmHg) at first MRI	47.4 ± 14	38.8 ± 8.6	**0.001**
RVP (mmHg) at last MRI	48.4 ± 15	39.2 ± 8.7	**0.001**
Tricuspid regurgitation* n (%)	16 (9.4)	11 (23.4)	**<0.001**
PRF (%) at first MRI	33.2 ± 14.4	43 ± 10.	**<0.001**
PRF (%) at last MRI	34 ± 14.	43.7 ± 11.5	**<0.001**
% PRF change/year	0 (-1.9; -1.8)	0.25 (0.;4.5)	**0.01**
Cardiac events at follow-up	30 (18)	15 (31)	**0.04**

the contrary, the low incidence of sustained tachyarrhythmias compared to the literature[27,28] could be due to the fact that EFs of both ventricles were preserved in the majority of patients at the first MRI. This is in accordance with what was reported by other studies[29-32], which identified significantly depressed LVEF and RVEF as well as age at ToF repair (but not RVEDVi) as predictors of major adverse outcomes.

Male sex was associated with higher RV dimensions at the first MRI exam without significant differences in EFs. Such results appear in agreement with the evidence reported by Lee et al[33], that the male sex is an independent predictor for RV dilatation. Moreover, males had an annual worsening of RVEF, albeit minimal, with the same annual growth in RV size compared to females. On this basis, even considering the larger dimensions of both ventricles documented at the first MRI as a consequence of different body conformation, our belief remains that sex should be taken into consideration when evaluating a patient with rToF, and even more so for PVR indication, given that the adaptive response to chronic volume overload appears different between the two sexes[13,33-36].

Limitations

We could not derive any conclusions regarding the impact of varying degrees of pulmonary regurgitation on RV volume progression, since almost all our patients had a PRF ≥ 20%. The time interval between MRI studies was not the same for all patients. To overcome this issue, we

Table IV. Comparison between patients younger and older than 18 years. Legend: BSA=Body Surface Area; TP=transannular patch; RVEDVi=right ventricle end-diastolic volume indexed to BSA; RVESVi=right ventricle end-systolic volume indexed to BSA; RVEF=right ventricle ejection fraction; LVEDVi=left ventricle end-diastolic volume indexed to BSA; LVESVi=left ventricle end-systolic volume indexed to BSA; LVEF=left ventricle ejection fraction; RVP=right ventricle pressure; Tricuspid regurgitation*=more than moderate; PRF=pulmonary regurgitation fraction.

Parameters	Age <18 years (n=122)	Age ≥ 18 years (n=97)	*p*-value
Age (years)	12.9 ± 2.0	29.5 ± 8.4	**<0.001**
Time First-Last MRI (years)	4.6 ± 2.3	5 ± 2.6	0.23
BSA	1.4 ± 0.24	1.7 ± 0.19	**<0.001**
Male n (%)	64 (52)	52 (53.6%)	0.4
Age at repair (years)	7.73 (5.56; 12.3)	33.3 (16.7; 60.6)	**<0.001**
Previous shunt n (%)	15 (12.5)	43 (44.8)	**<0.001**
TP n (%)	113 (92.6)	69 (71)	**0.02**
NYHA (II/III) n (%)	2 (1.6)	12 (12)	**< 0.01**
QRS (msec)	128 ± 25	144 ± 25	**<0.001**
RVEDVi (ml/m^2) at first MRI	131 ± 27	134 ± 39	0.51
% RVEDVi change/year	1.4 (-0.63; 4.4)	0.24 (-1.1; 2)	**0.008**
RVESVi (ml/m^2) at first MRI	57.6 ± 18	63 ± 22	0.07
% RVESVi change/year	2.25 (-0.49; 7.7)	1.27 (-0.43; 4)	0.09
RVEF (%) at first MRI	57 ± 5.8	53.3 ± 5.8	**<0.001**
% RVEF change/year	-0.89 (-2.2; 0.33)	-0.38 (-2; 0.97)	0.71
LVEDVi (ml/m^2) at first MRI	78.2 ± 11.8	79.1 ± 13.6	0.6
% LVEDVi change/year	0.87 (-1.46; 2.9)	-0,2 (-2.9; 2.6)	**0.003**
LVESVi (ml/m^2) at first MRI	30.4 ± 6.6	32 ± 8.7	0.1
% LVESVi change/year	2.6 (-0.88; 7.9)	0.02 (-3; 2.66)	**<0.001**
LVEF (%) at first MRI	60.7 ± 5.2	60.6 ± 6.1	0.91
% LVEF change/year	0.92 (-2.5; 0.49)	-0.48 (1.59; 0.7)	0.11
RVP (mmHg) at first MRI	45.5 ± 14.7	43.2 ± 11	0.46
Tricuspid regurgitation* n (%)	17 (14)	10 (10.5)	0.41
PRF (%) at first MRI	38 ± 11.1	32.1 ± 17	**<0.01**
% PRF change/year	0 (-1.96; 0.52)	0.36 (-0.5; 4)	**0.01**
Cardiac events at follow-up	9 (7.8)	36 (37)	**<0.01**

divided the total growth of RV between the first and the last exam by the total number of years between the two MRIs in order to have the annual growth. However, Also, we did not take into consideration cardiopulmonary exercise stress data (CPET). Therefore, we cannot make any final considerations about the impact of severe RV dilation on exercise performance. In addition, our population includes patients with severe RV dilation and mainly preserved or minimally reduced RVEF and LVEF. Therefore, this may have led to an underestimation of adverse events.

Conclusions

Changes in RV dimensions and function occur rarely and very slowly in rToF patients, even in the presence of significant RV dilation. Adverse events occur uncommonly and late during follow-up after rToF and do not appear to correlate with the volumes and function changes per year. Therefore, a delay in PVR should be considered in selected young patients with a low risk of significant progression of RV size and normal biventricular function.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

B.L. and L.A.A. conceived and designed the experiments; B.L and, L.A.A. drafted the manuscript; F.G., A.S., D.C., M.A.P., M.C. (Marcello Chinali) and B.L. visited the patients and conducted the clinical and imaging tests; C.M. and F.G. collected the data; L.A.A. and M.B. analyzed the data; A.C., M.G.G., M.A.P., L.G., F.D., P.F., M.C. (Massimo Caputo), R.W. and B.L. supervised the final manuscript.

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Table V. Comparison between males and females. Legend: BSA=Body Surface Area; TP=transannular patch; RVEDVi=right ventricle end-diastolic volume indexed to BSA; RVESVi=right ventricle end-systolic volume indexed to BSA; RVEF=right ventricle ejection fraction; LVEDVi=left ventricle end-diastolic volume indexed to BSA; LVESVi=left ventricle end-systolic volume indexed to BSA; LVEF=left ventricle ejection fraction; RVP=right ventricle pressure; Tricuspid regurgitation*=more than moderate; PRF=pulmonary regurgitation fraction.

Parameters	Female (n=103)	Males (n=116)	*p* value
AAge (years)	19.9 ± 9.6	20.5 ± 10.5	0.62
Time First-Last MRI (years)	5.1 ± 2.6	4.6 ± 2.3	0.09
Age at repair (months)	12.7 (6.7; 33.1)	12 (6.45;2 5.5)	0.8
Previous shunt (n;%)	31 (30.4)	27 (23.7)	0.26
TP (%)	84 (81.6)	98 (84.5)	0.56
NYHA (II/III) n (%)	10 (9.9)	4 (3.6)	0.09
QRS (msec)	131 ± 27.8	138 ± 25	**0.04**
RVEDVi (ml/m2) at first MRI	124.0 ± 30.5	139 ± 33.4	**0.001**
% RVEDVi change/year	0.82 (-0.6; 3)	0.71 (-1;5.3.1)	0.63
RVESVi (ml/m2) at first MRI	55.2 ± 17.8	64.2 ± 21.4	**0.01**
% RVESVi change/year	1.48 (-0.43; 4)	2.1 (-0.76; 6)	0.74
RVEF (%) at first MRI	56.0 ± 6.3	54.5 ± 5.7	0.06
% RVEF change/year	-0.37 (-1.785; 0.73)	-0.96 (-2.7; 0.3)	**0.03**
LVEDVi (ml/m2) at first MRI	75.6 ± 12.4	81.2 ± 12.2	**0.001**
% LVEDVi change/year	0.86 (-1.89; 3.26)	0.26 (-1.7; 3)	0.34
LVESVi (ml/m2) at first MRI	29.4 ± 6.7	32.6 ± 8.1	**0.002**
% LVESVi change/year	1 (-1.9; 3.2)	2.1 (-2; 9.1)	0.15
LVEF (%) at first MRI	61 ± 5.4	60.5 ± 5.8	0.48
% LVEF change/year	-0.58 (-1.9; 0.37)	-0.86 (-2.5; 0.52)	0.29
RVP (mmHg) at first MRI	44.6 ± 13.2	44.7 ± 12.9	0.78
Tricuspid regurgitation* (%)	11 (10.7)	16 (14)	0.7
PRF (%) at first MRI	34.5 ± 15	36 ± 13.3	0.53
% PRF change/year	0.0 (-1.03; 2.5)	0 (-2; 2.2)	0.09
Cardiac events at follow-up	17 (17.5)	27 (24)	0.1

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