Right ventricular dilatation in patients with pulmonary regurgitation after repair of tetralogy of Fallot: How fast does it progress?

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ABSTRACT

Objective : **Pulmonary valve regurgitation (PR) and right ventricular (RV) dilatation are important residual findings after surgical repair of tetralogy of Fallot (TOF). We sought to describe the natural course of RV dilatation over time in patients with severe PR after TOF repair and to determine risk factors for quick progression of RV dilatation and dysfunction.**

Methods : **Data of 85 consecutive TOF patients with PR and RV dilatation, undergoing serial cardiovascular magnetic resonance (CMR) scans between July 2002 and December 2016 in two institutions, were retrospectively reviewed. The dataset was analyzed regarding right and left ventricular (LV) volume and function and potential risk factors of progressive RV dilatation**

Results : **There was no significant increase in RV end-diastolic volumes ($RVEDV_i$) indexed body surface area (BSA) (median 150 [81–249] vs. 150 [82–260] mL/m²) and end-systolic volumes indexed for BSA ($RVESV_i$) (75 [20–186] vs. 76 [39–189] mL/m²) between the first and last CMR in the overall group. Similarly, there were no significant changes in LV volumes indexed for BSA ($LVEDV_i$ 78 [56–137] vs. 81 [57–128] mL/m² and LV end-systolic volume index 34 [23–68] vs. 35 [18–61] mL/m²). Global function remained also unchanged for both ventricles. $RVEDV_i$ increased statistically significantly (≥20 mL/m²) in twenty patients (24%) from 154 mL/m² (87–237) to 184 mL/m² (128–260, $P < 0.001$). LV dimensions showed a similar trend with LVEDVi increase from 80 ml/m² (57–98) to 85 ml/m² (72–105, $P = 0.002$). Shorter time interval between repair and first CMR was the only risk factor predictive for progressive RV dilatation.**

Conclusion : **In the majority of patients with repaired TOF and severe PR, RV dilatation is unchanged during a follow-up of 3 years. RV dilatation seems to progress early after surgery and subsequently stabilize. RV dilatation significantly progresses in a subgroup of 24% of patients, with a shorter time interval since surgical repair.**

Keywords : Pulmonary regurgitation, pulmonary valve replacement, right ventricular dilatation, tetralogy of Fallot

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INTRODUCTION

Pulmonary valve regurgitation (PR) is an important residual finding after surgical repair of tetralogy of Fallot (rTOF). Severe PR causes progressive right ventricular (RV) dilatation, with a potential negative cascade including RV dysfunction, deterioration of physical performance, life-threatening arrhythmias, and eventually premature death.[1,2] Thanks to new interventional techniques, there is currently a trend for timely insertion of a new pulmonary valve.[3] However, the correct timing for pulmonary valve replacement (PVR) is still a subject of debate, and little is known about the progression rate of RV dilatation. With growing interest in the early identification of deteriorating ventricular volumes, clinical guidelines recommend serial cardiovascular magnetic resonance (CMR) every 2–3 years.[4] However, still, there are inconsistent observations, with some studies showing progression of RV dilatation over time in rTOF patients and others indicating stable parameters in the overall population.[5-8] As an alternative to the idea of a continuous RV dilatation, there is some evidence suggesting that the RV dimensions may enlarge soon after repair and remain almost unchanged during longer follow-up.[9]

This study was aimed to describe the natural course of RV dilatation over time in patients with PR after TOF repair, as measured by serial CMR, and to determine potential risk factors for quick progression of RV dilatation and dysfunction.

METHODS

Population

Data of all consecutive rTOF patients with PR and RV dilatation, undergoing serial CMR scans between July 2002 and December 2016 in two institutions (University Children's Hospital Zurich, Switzerland; Bambino Gesù Children's Hospital, Rome, Italy), were retrospectively reviewed. Demographic and clinical data were recorded from the medical records and included gender, diagnosis, age at surgical repair, surgical technique, and age and body surface area (BSA) at the time of each CMR.

Inclusion criteria were diagnosis of TOF and its variants, including pulmonary atresia with ventricular septal defect and double-outlet right ventricle of Fallot type, and at least two consecutive CMR examinations in the same patient, without any intervention in between.

Exclusion criteria were diagnosis of pulmonary atresia with intact ventricular septum, surgical repair at age ≥30 years, and incomplete CMR dataset.

CMR technique

In Zurich, CMR scans were performed with a 1.5 T systems (Signa MR/i Twinspeed or Discovery MR 450, GE Medical Systems, Waukesha, Wisconsin, USA) using phased-array cardiac coils. After obtaining coronal, sagittal, and axial localizers, steady-state free precession (SSFP) cine images were acquired in a horizontal and vertical long-axis plane, as well as in a short-axis plane covering both ventricles from the base (plane of the atrioventricular valves) to the apex. Slice thickness was 5–8 mm with a gap of 0–2 mm as appropriate for body size for obtaining a total of 12–13 slices. All images were acquired during breathholding. The parameters of the SSFP sequence were as follows: 20 phases/cardiac cycle, echo time (TE) 1.5–1.8 ms, repetition time (TR) 2.8–3.1 ms, flip angle 45°, bandwidth 125 kHz, matrix 224 × 224, number of excitations 1, field of view 250–350 mm, views per segment 6–12 depending on heart rate, and retrospective cardiac gating.

In Rome, CMR examinations were performed with a 1.5 T scanner (Achieva, Philips Medical, Best, The Netherlands) using a five-channel phased-array cardiac coil and an identical imaging protocol. The parameters of the SSFP sequence were as follows: 30 phases/cardiac cycle, TE 1.45 ms, TR 2.9–3.3 ms, flip angle 60°, bandwidth 1750 kHz, acquisition matrix 164 × 162, number of averages 1, field of view 250–350 mm, views per segment 10–13 depending on heart rate, and retrospective cardiac gating.

All images were postprocessed on commercially available workstations, and ventricular parameters were calculated with dedicated cardiac software (Mass Versions 4–8, MEDIS, Medical Imaging Systems, Leiden, The Netherlands, and Viewform, Philips Medical, Best, The Netherlands, respectively, as previously described.[10] All ventricular parameters were indexed for BSA.

Moderate PR was defined as a regurgitation fraction of ≥20%. Definitions of RV dilatation, normal RV ejection fraction (EF) % ≥50, and left ventricular (LV) EF % ≥55 were based on the existing normal values.[10-13]

Similarly, the published variability of CMR measurements helped to define a significant difference in ventricular volume, if this changed more than 10% of its initial value; thus, we defined a significant progression in RV dilation if the RV end-diastolic volume indexed ($RVEDV_i$) increased by more than 20 ml/m^2.[10]

Statistical analysis

Contiguous data were reported as median and range. Categorical data were expressed as percentage. Data were tested for normality using the D'agostino and Pearson's normality test. As not all data were normally distributed, nonparametric tests were chosen for the statistical analysis.

Changes of the ventricular parameters over time were tested with the Wilcoxon signed-rank test. All data of the group with significant $RVEDV_i$ progression (≥20 ml/m²) were compared with the same data of the group without significant $RVEDV_i$ progression (≤20 ml/m²). Continuous parameters were compared using the Mann–Whitney U-test. Categorical data were tested with the Chi-square test and the Fisher's exact test. The correlation between RV end-diastolic volume (RVEDV) changes over time and continuous parameters was assessed with the Spearman's rho correlation coefficient. These parameters included age at surgical repair, surgical technique used for repair, age at first CMR, time from surgical repair to first CMR, LV volumes and biventricular function at first CMR, and BSA changes.

The results were two tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS Inc., Version 22.0 (Chicago, IL, USA) and Graphpad Prism Inc., Version 5 (San Diego, CA, USA) software.

The study was approved by the ethical authorities of both institutions.

RESULTS

Demographics

Eighty-five consecutive patients (39 females) with PR and RV dilatation who underwent at least two (range 2–6) CMR examinations, without having any intervention between the first and last CMR scan, were included in the study. The diagnosis was repaired TOF in 80, double-outlet right ventricle of Fallot type in three, and pulmonary atresia (PA) with ventricular septal defect in two patients. Patient characteristics are presented in Table 1.

Surgical repair was performed at a median age of 1 year (2 months–12 years). The RV outflow tract had been reconstructed using the transannular patch technique in 57 (67%) patients, an infundibular patch in 8 (9%), a commissurotomy with infundibular resection in 5 (6%), and an isolated insertion of a homograft in 9 (11%) patients. The operation technique was unknown in six patients (7%).

The first CMR examination was performed at a median age of 13.7 (1.4–45) years, corresponding to 12.6 (1–40) years after surgery. The last CMR examination was taken at a median age of 18.3 (7 months–49 years) years. The median time interval between the first and last CMR scans was 3.4 (6 months–12.2 years) years. There was no significant difference between the time interval in the progression group (3.2 years [6 months–11.5 years]) versus the stable group (4 years [1.3 years–12.2 years]).

Two-thirds (62%) of all patients were younger than 16 years at the first CMR, and 40% at the last CMR examination.

Ventricular volumes

The volumes of both ventricles at the time of first CMR are shown in Table 2. There was significant RV dilatation with a median RVEDV of 150 ml/m² (81–249). During follow-up, no significant increase in RV or LV dilatation was observed in the overall patient group [Table 2].

$RVEDV_i$ increased significantly (≥20 mL/m²) in twenty patients (24%) [Figure 1]. The median increase for $RVEDV_i$ from 154 mL/m² (87–237) to 184 mL/m² (128–260) [Table 3], corresponded to the annual increase rate of 8 ml/m²/years (2–28) for the RVEDV. Interestingly, in this group, $RVESV_i$ and LV volume indexed, but not LV end-systolic volume index, significantly enlarged as well [Table 3]. Both ventricles did not show any changes in EF%.

Factors related to progressive right ventricular dilatation

The shorter time interval between repair and first CMR was related to progressive RV dilatation, being

Table 1: Patient characteristics of the overall population and progressive dilatation and nonprogression groups

	Overall population (*n*=85)	Progressive dilatation group (*n*=20)	Nonprogression group (*n*=65)
Gender female	39	8	31
Age at first CMR	13.7 (1-45)	13 (1-43)	13.7 (3-45)
Time of surgery to first CMR	12.6 (1-40)	11.1 (1-40)	13.2 (3-40)
Number of CMR examinations	2 (2-6)	3 (2-4)	2 (2-6)
Diagnosis			
TOF	80	19	61
DORV (Fallot type)	3	0	3
PA/VSD	2	1	1
Type of repair			
Transannular patch	57	13	44
Infundibular patch	8	1	7
Commissurotomy with infundibular resection	5	3	2
Homograft	9	2	7
Unknown	6	1	5

CMR: Cardiac magnetic resonance, TOF: Tetralogy of Fallot, DORV: Double-outlet right ventricle, PA/VSD: Pulmonary atresia/ventricular septal defect

11.1 (12 months–40 years) years in the group with significant RVEDV increase, compared to 13 (3–40) years in the group without progressive RV dilatation ($P = 0.03$) [Figure 2]. In contrast, presence of a transannular patch, initial RV volume, BSA changes, LV volumes and biventricular function at first CMR, and age at repair were not associated with a significant progression of RV dilatation.

Table 2: Cardiac magnetic resonance volumetric parameters (indexed) of the overall population (*n*=85)

	First CMR	Last CMR	*P*
$RVEDV_i$ (ml/m²)	150 (81-249)	150 (82-260)	0.11
$RVESV_i$ (ml/m²)	75 (20-186)	76 (39-189)	0.31
RVEF (%)	49 (22-68)	50 (18-68)	0.72
$LVEDV_i$ (ml/m²)	78 (56-137)	81 (57-128)	0.17
$LVESV_i$ (ml/m²)	34 (23-68)	35 (18-61)	0.45
LVEF (%)	57 (43-70)	57 (40-71)	0.62

CMR: Cardiac magnetic resonance, BSA: Body surface area, $RVEDV_i$: Right ventricular end-diastolic volume indexed for BSA, $RVESV_i$: Right ventricular end-systolic volume indexed for BSA, RVEF: Right ventricular ejection fraction, $LVEDV_i$: Left ventricular end-diastolic volume indexed for BSA, $LVESV_i$: Left ventricular end-systolic volume indexed for BSA, LVEF: Left ventricular ejection fraction

Table 3: Cardiac magnetic resonance parameter of the dilatation group (*n*=20)

	First CMR	Last CMR	*P*
$RVEDV_i$ (ml/m²)	154 (87-237)	184 (128-260)	<0.001
$RVESV_i$ (ml/m²)	83 (23-186)	96 (58-189)	<0.001
RVEF (%)	49 (22-62)	46 (27-58)	0.69
$LVEDV_i$ (ml/m²)	80 (57-98)	85 (72-105)	0.002
$LVESV_i$ (ml/m²)	34 (23-53)	40 (26-61)	0.099
LVEF (%)	55 (44-67)	56 (42-66)	0.48

CMR: Cardiac magnetic resonance, BSA: Body surface area, $RVEDV_i$: Right ventricular end-diastolic volume indexed for BSA, $RVESV_i$: Right ventricular end-systolic volume indexed for BSA, RVEF: Right ventricular ejection fraction, $LVEDV_i$: Left ventricular end-diastolic volume indexed for BSA, $LVESV_i$: Left ventricular end-systolic volume indexed for BSA, LVEF: Left ventricular ejection fraction

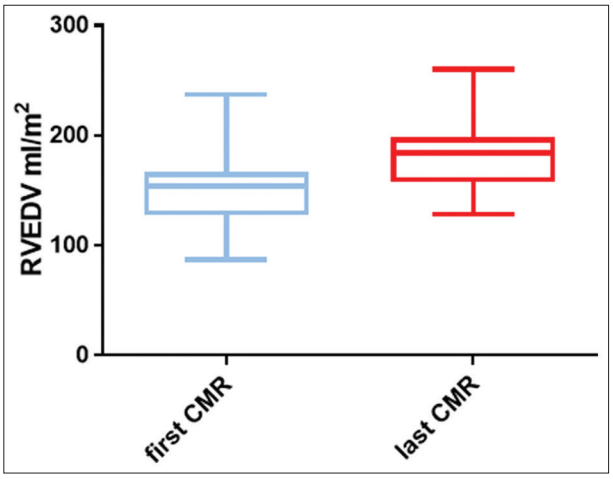

Figure 1: Box and whiskers plots comparing changes in indexed right ventricular end-diastolic volume between first and last CMR of the progressive dilatation group (*n* = 20), RVEDV = Right ventricular end-diastolic volume, CMR = Cardiac magnetic resonance

DISCUSSION

The present study shows that RV volumes significantly increase in only 24% of the patients, over an average time period of 3.4 years. In this patient subgroup, the annual rate of increase was small and RV EF remained preserved. The only factor related to progressive RV enlargement was the time interval between surgical repair and the CMR examination. This observation supports the idea of Greutmann that RV dilatation represents an early postoperative remodeling after TOF repair, which tends to remain stable during follow-up, as we have observed for the overall group of patients.[9]

These results are in line with two other previous studies reporting no significant progression in the majority of rTOF patients[5,6] and consolidate the opinion that indication for PVR should be carefully pondered, including follow-up data in asymptomatic patients in order to detect the individuals in whom RV deterioration may occur.

The ideal timing for PVR in asymptomatic rTOF patients with severe PR and RV dilatation is still the subject of debate. Although previous data have shown prompt RV remodeling with decrease in RV volumes and mass after PVR,[14-16] a positive impact of PVR on outcome could not yet be demonstrated.[17] Bokma *et al.* analyzed the data of the INICATOR study to test the impact of PVR on clinical outcome.[18] Predefined guideline criteria for PVR were classified into "proactive" or "conservative" on the basis of the available literature and by consensus of the authors, and were used to determine the impact of PVR on outcomes. The study showed that PVR did not reduce the rate of death and/or sustained ventricular tachycardia (VT) during a follow-up of 5.3 years. In addition, greater number of clinical adverse events occurred, if PVR was performed in patients not meeting the consensus criteria.

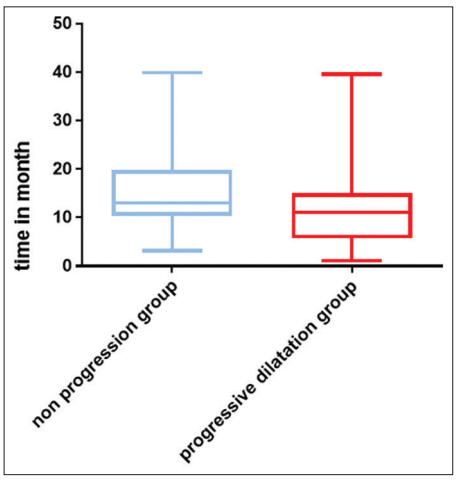

Figure 2: Time interval between repair and first CMR in nonprogression (*n* = 65) and progressive dilatation groups (*n* = 20). CMR = Cardiac magnetic resonance

Other recent data have shown that early favorable RV remodeling is followed by recurrent gradual RV enlargement toward pre-PVR values with a decline in global RV systolic function. This late adverse remodeling becomes relevant 7–10 years after implantation and is associated with increasing regurgitation and stenosis of the new bio-prosthetic pulmonary valve.[19] Percutaneous PVR is significantly less invasive than surgery and provides excellent short-term results; thus some advocate a more timely insertion of a new pulmonary valve in these patients.[20] However long-term results of valvular function after percutaneous PVR are not available yet. Meanwhile, an elevated prevalence of infective endocarditis after percutaneous pulmonary valve insertion has been reported; this seems to be higher than that in homograft valves and may be considered as an additional caveat for unnecessary PVR.[21]

For all these reasons, the definition of the correct timing for PVR in rTOF patients remains a conundrum in modern congenital cardiology. On the basis of the results of our article and others,[5,6] the real challenge is to define the risk factors predicting a progressive RV deterioration and thus to recognize the correct patients for an early PVR. The evidence from the literature regarding this aspect is controversial. Even though some previous publications advocate the negative effect of the presence of a transannular patch, Rutz *et al.* did not describe any influence of different surgical techniques used for repair (transannular patch, subvalvular patch, and isolated infundibulectomy),[5] neither did we. Wald *et al.* reported the presence of a RV/PA conduit, higher RV volumes at baseline CMR, and lower EF% as predictors for RV deterioration.[6] In our smaller group of patients, we could not observe these findings. The inconsistency of the predictive factors reported in the literature may indicate that the RV volume alone may not be a sufficient parameter for selecting patients needing PVR.

There is increasing evidence that LV parameters deserve more attention. The INDICATOR study has provided the first robust data for risk stratification of patients after TOF repair.[1] Not only RV hypertrophy and dysfunction but also LV dysfunction was a strong predictor for adverse outcome.[1] Dragulescu *et al.*, using speckle tracking, found that LV myocardial deformation is decreased in rTOF patients despite a preserved LV EF%.[22] Similarly, Orwat *et al.*, by using CMR-based feature tracking (FT) analysis, showed that LV strain is a significant predictor for life-threatening events or death in these patients, and its predictive value is superior to that of LV EF%.[23] With the retrospective design of our study, strain measurements of the left ventricles could not be performed; LV dilatation was observed in parallel to RV dilatation in the group with progressive dilatation, suggesting some unfavorable interventricular interaction [Table 3].

Novel imaging modalities provide additional subtle parameters which may help to identify patients at risk. Hanneman *et al.* measured the myocardial extracellular volume (ECV) by using CMR in adult rTOF patients and found a correlation between an increased RV ECV and major adverse cardiovascular events.[24] CMR assessment of dyssynchrony and biventricular myocardial fibrosis showed that PVR reduces RV volumes, but has no effect on these two parameters.[25,26]

Considering the increasing amount of available data, future direction of investigation should include many different imaging and bio-parameters, in order to understand the precise mechanisms that trigger unfavorable RV remodeling such as fibrosis, progressive RV enlargement, and function deterioration.[27] Hence, recently, Samad *et al.* used machine learning and applied different regression models to baseline variables of 153 patients, for demonstrating that prediction of RV volume and function deterioration requires the inclusion of at least six baseline parameters, with LV being one of the most important.[28] The proof of this new approach has the potential of giving new insights regarding meaningful clinical decision-making and a potential paradigm change. Therefore, based on the current evidence from the literature, the optimal timing for interventions should be defined on the basis of multiple parameters, including clinical and functional status, conventional biventricular CMR parameters and novel imaging biomarkers, arrhythmias, and possibly up to genetic biomarkers.[27]

Limitations

This study has the limitation of being retrospective. Our population consisted of TOF cases mostly referred for advanced CMR imaging from outside referral centers. Thus, we had only limited influence on the subsequent clinical decision-making regarding a PVR, what allowed us to sequentially examine patients with a significantly dilated RV. On the other hand, we had only limited access to clinical information such as functional status, exercise capacity, and presence of arrhythmias, so that with our data, we cannot draw any conclusions on the influence of progressive RV dilatation on outcome.

Advance d image analysis, such as FT, was restricted by the multicentric design, with not totally homogenous imaging parameters, which was a limitation particularly regarding temporal resolution.

Volumetric changes during follow-up may represent variability of the measurements. We have obviated this potential source of error, by defining a significant change to be more than 20 ml/m^2, corresponding to >10% of the value, which represents a sufficient range, based on the inter- and intra-observer variabilities of CMR volume measurements in rTOF patients previous published by our group.[11]

CONCLUSIONS

The vast majority of patients with PR after TOF repair and a dilated RV does not experience progressive RV dilatation during a follow-up of 3 years. RV dilatation appears to progress early after surgery and to subsequently stabilize. There is no evidence that surgical technique may influence the progression of dilatation. As RV progression is slow and function stable, a more conservative approach with follow-up imaging before PVR may be justified in clinically asymptomatic patients. The mechanisms triggering a progressive RV dilatation remain unclear.

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Conflicts of interest

There are no conflicts of interest.

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