Right ventricular function in patients with pulmonary regurgitation with versus without tetralogy of Fallot

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Background Right ventricular (RV) dilation from pulmonary valve regurgitation (PR) is common after intervention(s) for pulmonary stenosis (PS) or atresia and intact ventricular septum (PA/IVS). It is not well established whether PR and RV dilation have similar effects on RV function and exercise capacity in these patients compared to patients after repair of tetralogy of Fallot (rToF). The aims of this study were to compare exercise tolerance, RV function and myocardial mechanics in non-ToF versus rToF children with significantly increased and comparable RV volumes.

Methods Thirty PS or PA/IVS children after intervention(s) with significant PR and RV dilation (non-ToF group) were retrospectively matched for RV end-diastolic volume index (RVEDVi) and age with 30 rToF patients. Clinical characteristics, RV function by echocardiography and CMR, ECG and exercise capacity were compared between groups.

Results The groups were well matched for RVEDVi and age. Global RV function (RVEF: 48.7 ± 6.4% vs. 48.5 ± 7.2%, $P = .81$) and exercise capacity (% predicted peak VO_2:82.5 ± 17.7% vs. 75.6 ± 20.4%, $P = .27$) were similarly reduced between groups. RVEDVi correlated inversely with RVEF in both groups (non-ToF:r = –0.39, $P = .04$, rToF:r = –0.40, $P = .03$). QRS duration was wider in rToF patients, and in both groups inversely correlated with RVEF (non-ToF:r = –0.77, $P < .001$, rToF:r = –0.69, $P < .001$). In contrast to global function, longitudinal RV strain was lower in rTOF vs non-TOF (–20.1 ± 3.9 vs.-25.7 ± 4.4, $P < .001$).

Conclusions Global RV function and exercise capacity are similarly reduced in non-ToF and rToF patients with severely dilated RV, after matching by RVEDVi, suggesting a comparable impact of RV dilation on RV global function. The significance of reduced RV longitudinal function and worse dyssynchrony in rToF patients require further exploration. (Am Heart J 2019;213:8-17.)

Pulmonary valve regurgitation (PR) is common after tetralogy of Fallot repair (rToF)[1] but is also prevalent in other congenital heart diseases, such as after balloon dilation of isolated pulmonary stenosis (PS)[2] and after surgical or percutaneous intervention for pulmonary atresia with intact ventricular septum (PA/IVS).[3] Chronic PR exposes the right ventricle (RV) to increased volume loading and is considered a major driver of long-term complications after rToF including RV dilation and dysfunction, exercise intolerance, arrhythmias and sudden death.[4]

Pulmonary valve replacement (PVR) has emerged as a central therapy to ameliorate PR and its sequelae. Current indications for the timing of PVR are largely based on symptoms, electrocardiographic and cardiac magnetic resonance (CMR) imaging measures of RV size and function.[4-8] In asymptomatic patients, RV volume is a central factor in deciding when to replace the pulmonary valve. Although there is a lack of universal consensus on the exact threshold RV volume for PVR,[8] most studies have included predominantly rToF patients and whether the impact of RV dilation on RV function and exercise capacity (and hence criteria for PVR) is similar in non-ToF patients with chronic PR is not well known. Harrild et al found that even mild to moderate chronic PR after balloon dilation of isolated PS was inversely correlated with RV function and exercise capacity as measured by predicted peak exercise oxygen consumption (VO_2).[9] However, recent studies in both pediatric and adult populations comparing patients with PR after relief of pulmonary stenosis to rToF patients, have yielded conflicting results and have matched groups based on the amount of PR, rather than RV volume-which is the parameter used as an indication for PVR.[10-15]

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0002-8703
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https://doi.org/10.1016/j.ahj.2019.03.012

Non-ToF patients may differ from rToF patients in a number of ways including the duration and intensity of cyanosis in infancy, the degree of residual RV outflow tract (RVOT) obstruction or branch PS, the degree of RV hypertrophy, the presence of surgical infundibulotomy, right bundle branch block, ventricular septal defect patch, residual surgical scars, prosthetic or autologous tissue, severity of tricuspid valve regurgitation (TR), genetic factors and intrinsic RV myocardial properties.[4] These factors could potentially influence the RV response to PR, and consequently the degree of RV dilation and dysfunction. Consequently, the objectives of this study were to compare exercise tolerance, RV function and myocardial mechanics in non-ToF versus rToF children with clinically significant and comparable RV volumes.

Methods

This cross-sectional retrospective study was approved by the institutional Research Ethics Board and a waiver of consent was obtained. No extramural funding was used to support this work.

Study population

Non-TOF group. Children with isolated PS or PA/IVS after percutaneous or surgical PV interventions who underwent CMR imaging between 2006 and 2016, were included if they had more than mild PR (defined as PR fraction (PRF) >15%)[9] and RV dilation (indexed RV end-diastolic volume (RVEDVi) >110 ml/m^2).[16] Patients with more than mild PS (RVOT gradient >25 mmHg), distal pulmonary artery stenosis and consequent RV hypertension (RV systolic pressure >50 mmHg by TR Doppler assessment where available)[17] were excluded. Patients with other complex congenital heart defects (eg, Ebstein anomaly) or significant intracardiac shunts were excluded if an additional procedure was required to close the defect after the initial intervention.

Repaired ToF patients. Each non-ToF patient was paired with a rToF control who had undergone CMR, matched by RVEDVi (within 15 ml/m^2) and then by age (within 2-years). The same exclusion criteria were applied to rToF patients.

Demographic, clinical and procedure data

Demographic and clinical information including gender, genetic disorders, age at procedure, and details of the RVOT intervention were obtained from the clinical records.

Cardiac magnetic resonance (CMR) imaging

The most recent CMR (or the most recent CMR before PVR when applicable) was analyzed in both non-ToF and rToF groups. CMR was performed on a 1.5 T scanner ("Avanto" Siemens Medical Systems, Erlangen, Germany). The protocol included a cine short-axis stack for quantification of ventricular volumes, mass and ejection fraction and main pulmonary artery (MPA) phase contrast flow velocity mapping. CMR data were analyzed using commercially available software (Mass Analysis and CV Flow, Medis Medical Imaging Systems, Leiden, The Netherlands). Measurements recorded included RV and left ventricular (LV) end-diastolic, end-systolic volumes and stroke volume indexed to body surface area (BSA), ejection fractions (EF, %), indexed MPA forward, backward and net flows, and derived PRF (%). RV ejection fraction was used to assess RV global function, despite incorporating the RVEDVi used as the matching parameter, as this is the most commonly accepted parameter in practice and has previously been used in clinical trials addressing RV remodeling.[18]

Echocardiography

An echocardiogram closest in time with CMR was analyzed by a single operator, and the degree of TR was qualitatively classified taking into account the regurgitant jet width.[19] The peak RVOT systolic gradient and RV systolic pressure were assessed by continuous wave Doppler through the RVOT and TR jet, respectively. An arbitrary assumed right atrial pressure of 5 mmHg was added to the TR gradient as per clinical practice in our lab. Parameters of RV global (RV-fractional area change (FAC)), and longitudinal function (tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler imaging systolic velocity (S′) at the basal lateral and septal walls) were measured.[20] The presence of restrictive physiology, defined as anterograde pulmonary flow in late diastole throughout the respiratory cycle was recorded.[17]

RV longitudinal strain was measured offline using vendor-independent two-dimensional speckle-tracking analysis (TomTEC Image-Arena v4.6, Unterschleissheim, Germany) by a single observer (GL) from a RV-centered apical 4-chamber view DICOM image, with a frame rate of 50–100 fps. The software automatically tracked the myocardium and segmented the RV into 3 lateral wall and 3 septal segments. Tracking was accepted only when the software and the observer indicated adequate tracking. If more than 1 segment could not be tracked adequately, analysis of strain data from that patient was excluded. The peak longitudinal RV strain during the cardiac cycle by segment was recorded.

ECG

The ECG closest in time to the CMR was assessed. QRS duration (ms) and the presence of incomplete or complete right bundle branch block (RBBB) morphology were recorded.[21]

Cardiopulmonary exercise test

Cardiopulmonary exercise testing was performed using an upright bicycle and a modified Bruce protocol with standard metabolic measurements. Data from the closest

Table I. Matching variables, group and specific diagnosis characteristics.

	Non-ToF (n = 30)	rToF (n = 30)	*P*	PS (n = 22)	PA/IVS (n = 8)	*P* (PS vs PA/IVS)	*P* (PS vs rToF)
Matching variables							
RV end-diastolic volume index, ml/m^2	162.2 ± 32.4	163.2 ± 33.3	.34	165.6 ± 33.3	153 ± 29.9	.36	.94
Age at CMR, years	13.9 ± 2.9	13.8 ± 2.9	.73	14.7 ± 2.5	11.8 ± 3.13	**.02**	.24
Demographics							
Male Gender, n (%)	19 (63.3%)	14 (46.7%)	.30	15 (68%)	4 (50%)	.42	.16
Genetic syndrome, n (%)	2 (6.7%)	3 (10%)	1.0	2 (9.1%)	0	1	1
Height, cm	158.8 ± 15.8	153.1 ± 15.8	.17	161.8 ± 13.3	150.2 ± 18.6	.07	.19
Weight, kg	54.7 ± 19.6	50.0 ± 22.3	.39	56.4 ± 16.3	51.5 ± 27.0	.55	.68
Body surface area, m^2	1.54 ± 0.34	1.44 ± 0.40	.28	1.6 ± 0.3	1.45 ± 0.45	.35	.48
Pulmonary atresia, n (%)	8 (26.7%)	3 (10%)	.18	0	8 (100%)	<**.001**	.25
Procedure(s) information							
Age at intervention for RVOTO, months	3.2 ± 9.3	11.2 ± 7.2	**.001**	4.2 ± 10.5	0.08 ± 0.07	.08	**.04**
Percutaneous procedure as initial intervention	29 (96.7%)	2 (6.7%)	<**.001**	22 (100%)	7 (87.5%)	1	<**.001**
Cardiac surgery under CPB, n (%)	7 (23.3%)	30 (100%)	<**.001**	4 (18,2%)	3 (37,5%)	.35	<**.001**
RVOT surgical repair, n (%)	4 (13.3%)	30 (100%)	<**.001**	2 (9,1%)	2 (25%)	.28	<**.001**
Transannular patch	1 (3.3%)	19 (63.3%)	<**.001**	0	1 (12.5%)	.27	<**.001**
Valve Sparing/only Valvotomy	3 (10%)	8 (26.7%)	.18	2 (9,1%)	1 (12.5%)	1	.16
Conduit/Homograft	0	2 (6.7%)	.49	0	0	1	.5

CMR, Cardiac magnetic resonance; CPB, cardio-pulmonary Bypass; PA/IVS, pulmonary atresia with intact ventricular septum; PS, pulmonary stenosis; rToF, repaired tetralogy of Fallot; RV, right ventricle; RVOT, right ventricular outflow tract; RVOTO, right ventricular outflow tract obstruction; ToF, tetralogy of Fallot. Data are presented as n (%) for categorical variables and mean ± SD. Significant values ($P < .05$) are shown in bold typeface.

cardiopulmonary exercise test were recorded if performed within 2 years of the CMR. Peak VO_2, VO_2 at anaerobic threshold, peak heart rate and workload were recorded as a percentage of predicted results for patient sex and age.[22]

Statistical analysis

Variables were tested for normality using the Shapiro-Wilks method. Descriptive statistics were reported as mean ± SD or medians with interquartile ranges (IQR) where appropriate. Non-ToF patients were compared as a group to rToF patients using a paired t-test for matched variables and independent-samples *t* test or Kruskal-Wallis, for non-matched variables as appropriate. A subanalysis stratified for the diagnosis of PS, PA/IVS or rToF was performed using an independent-samples *t* test (PS vs PA/IVS) and one-way repeated measures ANOVA with the Bonferroni post hoc test. Associations between covariates of non-ToF vs rToF were assessed with Pearson's regression. The significance of the differences between 2 correlation coefficients was assessed using Fisher r-to-z transformation.[23] A $P < .05$ was considered statistically significant for all the tests. Data were analyzed using SPSS (version 24, SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

Thirty non-ToF patients with more than mild PR and a dilated RV were analyzed, 22 (83.3%) with PS and 8 (26.7%) with PA/IVS. After exclusion of 39 of 100 potentially eligible rToF patients (RVOT obstruction >25 mmHg (n = 38) and residual shunts (n = 1)) they were pairwise matched with 30 rToF patients, 3 of whom (10%) originally had ToF with pulmonary atresia. These patients were included as they suffer from similar long-term RV dilatation, dysfunction and consideration for PVR as rTOF patients. Demographic characteristics are summarized in Table I. Age, gender distribution, body surface area and presence of a genetic syndrome were similar between the groups. As expected, all rToF patients underwent cardiac surgery with cardiopulmonary bypass versus 23.3% of the non-ToF ($P < .001$). All except one of the non-ToF patients underwent percutaneous PV balloon dilation (plus radiofrequency perforation in 6 of 8 PA/IVS patients). Four patients required additional RVOT surgical intervention. rToF patients were older at the intervention to resolve RVOT obstruction (11.2 ± 7.2 vs. 3.1 ± 9.1 months, $P < .001$) and 63.3% required a trans-annular patch, compared with 3.3% of non-ToF patients ($P < .001$).

ECG and cardiopulmonary exercise test data (Table II)

ECG was available in 93.3% of the patients. Heart rate was similar between groups while QRS duration and the proportion with complete RBBB morphology were significantly higher in rToF vs. non-ToF patients.

A cardiopulmonary exercise test was analyzed in 21 patient-pairs. Differences were observed in endurance time and % predicted peak workload, with better

Table II. ECG and Cardiopulmonary exercise test data

	Non-ToF	rToF	*P*
ECG (n = 28)			
Time from CMR, days	42 (24–86.5)	67 (32.8–135.3)	.15
Heart rate, bpm	76.4 ± 13.0	77.1 ± 14.2	.95
QRS Width, ms	101 (86.5–118.5)	145 (125.5–152.5)	**<.001**
RBBB morphology	17 (56.7%)	28 (100%)	**.001**
Complete RBBB	8 (26.7%)	24 (80%)	**.001**
Cardiopulmonary Exercise test (n = 21)			
Time from CMR, days	53 (30–118)	90.5 (19–266.3)	.11
Endurance, minutes	10.2 (9.4–11.2)	8.1 (7.1–9.8)	**.006**
Peak VO_2, predicted %	85.2 ± 17.2	79.2 ± 21.6	.27
Peak VO_2 at AT, predicted %	90 ± 27.0	90.7 ± 22.2	.91
Peak HR, predicted %	88.3 ± 6.9	85.7 ± 7.2	.22
Peak workload, predicted %	86.1 ± 18.1	68.9 ± 12	**.002**

AT, Anaerobic threshold; CMR, cardiac magnetic resonance; RBBB, right bundle-branch block; rToF, repaired tetralogy of Fallot; ToF, tetralogy of Fallot; VO_2, oxygen consumption. Data are presented as n (%) for categorical variables and mean ± SD or median (interquartile range) for continuous variables. Significant values ($P < .05$) are shown in bold typeface.

performance in these variables of the non-ToF compared with rToF patients. There were no significant differences in the percent predicted peak VO_2, VO_2 at anaerobic threshold, or maximal exercise heart rate between the groups.

Echocardiography and RV myocardial deformation (Table III)

An echocardiogram was available in all patients, median time between CMR and echocardiogram 7 (IQR 0–55) days. A higher proportion of non-ToF patients had greater than moderate TR vs. rToF patients. rToF patients had a mildly higher (but still low per study inclusion criteria) RVOT gradient and RV systolic gradient. Global RV function measured by FAC was similar between groups. In contrast, longitudinal RV function, including TAPSE, TDI lateral and septal S′ velocities, were lower in rToF vs. non-ToF patients. RV peak longitudinal strain was lower in all segments in rToF vs. non-ToF patients ($P < .001$ for all). RV apical segments could only be adequately tracked in 4 pairs of patients and therefore excluded from analysis.

Cardiac magnetic resonance (Table III)

By study design, RVEDVi was similar between non-ToF and ToF groups. Likewise, CMR derived RVESVi and LV volumes were similar between groups. RVEDVi was >150 ml/m^2 in 12 (40%) of non-ToF and 11 (36.7%) of rToF patients ($P = 1.0$). There was a trend towards higher indexed MPA backward flow and PRF in rToF vs. non-ToF.

Global RV function, measured by RVEF or indexed stroke volume, was similar in non-ToF vs. rToF. A similar proportion of patients had RV dysfunction (RVEF <45%) in non-ToF and rToF patients. LV function was also comparable between groups, with a similarly high prevalence of LV dysfunction (defined as LVEF <55%) in 32.3% of non-ToF vs 38.7% rToF patients, $P = .84$.

Associations with ventricular size and function

Moderate correlations were found between RVEDVi and PRF and between RVEDVi and MPA retrograde flow in the non-ToF (r = 0.55, $P = .002$ and r = 0.62, $P = .001$ respectively) and rToF groups (r = 0.56, P = .001 and r = 0.66, P = .001 respectively). In both groups, RVEDVi correlated inversely with global RV functional parameters, both for echo (FAC: r = −0.45, $P = .02$ in non-ToF and r = −0.40, $P = .03$ in rToF, Figure 1A-B) and CMR (RVEF r = −0.39, $P = .04$ in non-ToF and r = −0.40, P = .03 in rToF, Figure 1C-D). The Pearson's correlation coefficients were similar between the groups, with no statistical differences using the Fisher r to z transformation. There was a similar and strong inverse correlation between RVEF and QRS duration in both groups (r = −0.77, $P < .001$ in non-ToF; r = −0.69, P < .001 in rToF, z = −0.62, $P = .54$, Figure 1E-F).

Subgroup analysis

Sub-analysis of the non-ToF group according to the diagnosis of PS vs. PA/IVS revealed similar RVEDVi, PRF (Figure 2, A-B) and RVEF (Figure 3C) and comparable results between each of these sub-groups and rToF patients. Likewise, no differences were observed in QRS duration, predicted peak VO_2 and RV longitudinal function parameters (TAPSE, FAC or RV strain) between PS and PA/IVS patients (Figure 3A-B and D-F). When comparing PS with rToF patients, QRS duration, TAPSE and RV strain remained significantly different, while predicted peak VO_2 and RV FAC were similar between these subgroups.

Discussion

The effect of chronic volume loading on RV size and function has not been well studied in non-ToF patients in comparison to rTOF patients. This study addresses this knowledge gap and shows that children with isolated PS

Table III. Echocardiographic and cardiac magnetic resonance data

	Non-ToF	rToF	*P*
Echocardiography (n = 30)			
TR ≥ moderate, n (%)	12 (41.9%)	3 (9.7%)	**.02**
RVOT gradient, mmHg	10.9 ± 4.3	14.2 ± 5.3	**.01**
RVSP, mmHg	25.2 ± 6.1	31.7 ± 7.3	**.01**
RV-FAC, %	41.5 ± 7.6	40.0 ± 6.9	.40
TAPSE, mm	22.0 ± 5.1	16.9 ± 2.1	**<.001**
RV Lateral S′, cm/s	12.6 ± 3.4	7.9 ± 1.2	**<.001**
Septal S′, cm/s	7.8 ± 1.2	6.9 ± 1.1	**.003**
RV Restrictive physiology, n (%)	10 (34.5%)	4 (13.8%)	.18
RV Longitudinal strain (n = 23)			
Septal wall, basal, (%)	−23 ± 5.2	−17.2 ± 3.1	**<.001**
Septal wall, mid, (%)	−22.6 ± 4.6	−17.8 ± 2.7	**<.001**
Septal wall, average, (%)	−22.5 ± 4.5	−17.8 ± 2.7	**<.001**
Free wall, basal, (%)	−29 ± 5.3	−22.2 ± 4.3	**<.001**
Free wall, mid, (%)	−25.1 ± 6.5	−17.6 ± 3.8	**<.001**
Free wall, average, (%)	−25.7 ± 4.4	−20.1 ± 3.9	**<.001**
RV-4C, average, (%)	−24.1 ± 4	−18.9 ± 3	**<.001**
Cardiac magnetic resonance, (n = 30)			
RV end diastolic volume index, ml/m^2	162.2 ± 32.4	163.2 ± 33.3	.34
Patients with RVEDVi >150 ml/m^2	12 (40%)	11 (36.7%)	1.0
RV end systolic volume index, ml/m^2	83.8 ± 23.6	84.9 ± 22.3	.82
RV stroke volume index, ml/m^2	78.4 ± 14.5	77.9 ± 15.8	.81
RV ejection fraction, %	48.7 ± 6.4	48.5 ± 7.2	.81
Patients with RVEF <45%	8 (27.6%)	7 (24.1%)	1.0
LV end diastolic volume index, ml/m^2	85.1 ± 15.5	84 ± 13.2	.81
LV ejection fraction, %	56.6 ± 6.2	55.6 ± 7.1	.74
Patients with LVEF <55%	10 (32.3%)	12 (38.7%)	.82
MPA forward flow, L/min/m^2	5.1 ± 1.6	5.6 ± 1.4	.18
MPA backward flow, L/min/m^2	1.8 ± 1.2	2.2 ± 0.9	.09
MPA net flow, L/min/m^2	3.3 ± 0.8	3.4 ± 0.8	.75
Pulmonary regurgitation fraction, PRF %	32.3 ± 13.1	38.3 ± 10.7	.08

AT, Anaerobic threshold; EF, ejection fraction; FAC, fractional area change; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle; RVEDVi, right ventricle end diastolic volume index; rToF, repaired tetralogy of Fallot; RV-4C, right ventricle 4 chambers; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure; S′, tissue Doppler systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation. Data are presented as n (%) for categorical variables and mean ± SD for continuous variables. Significant values ($P < .05$) are shown in bold typeface.

or atresia, with hemodynamically significant PR and RV dilation after surgical or percutaneous intervention, have similarly reduced global RV function (RVEF, indexed RV stroke volume, FAC) and diminished exercise capacity compared to rToF children when matched by indexed RV end-diastolic volume.

RV dilatation

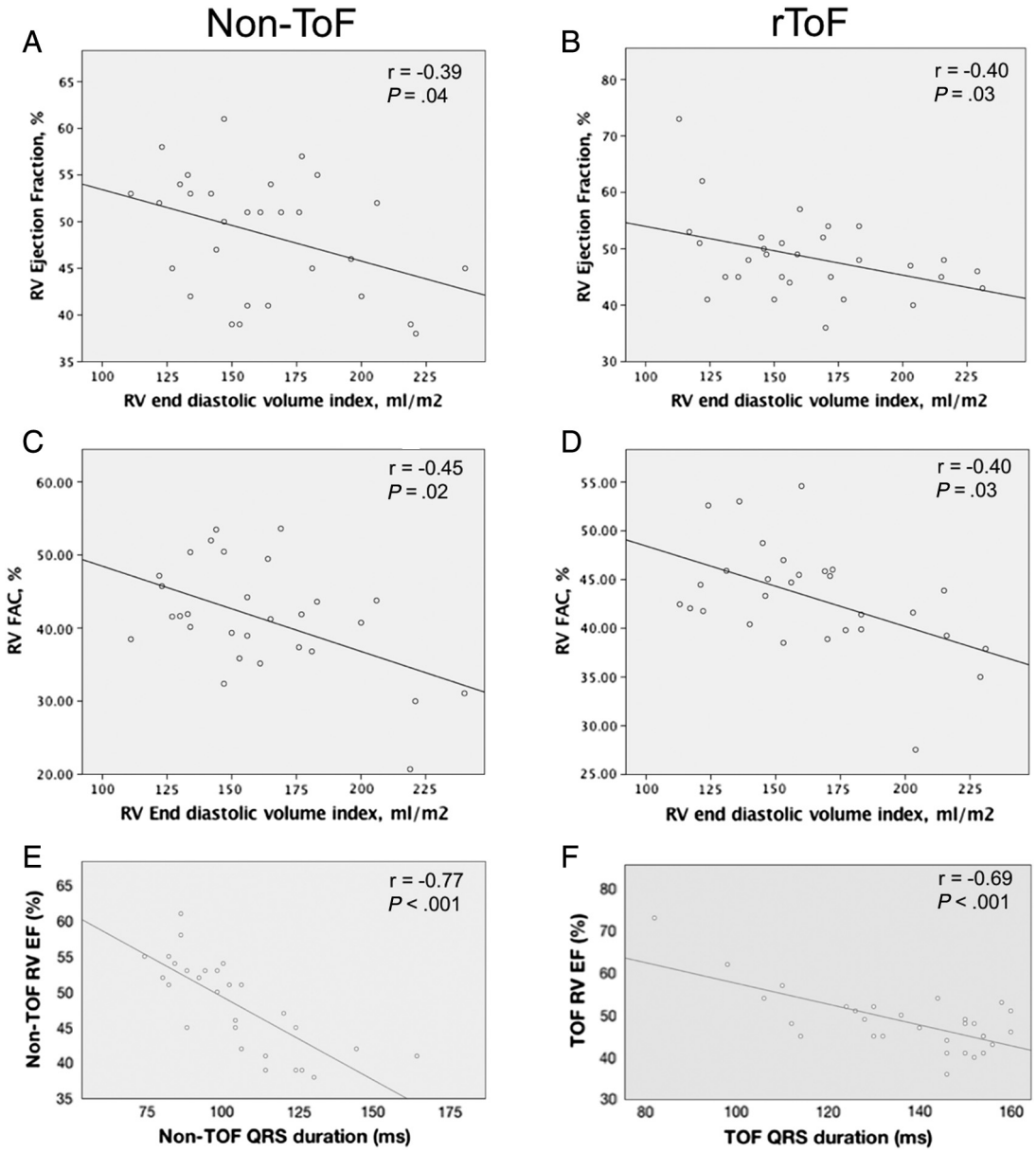
RV dilatation is a risk factor for development of ventricular dysfunction in rToF.[24] We found a moderate inverse correlation between RVEF and RVEDVi in both rToF and non-ToF, suggesting a comparable impact of RV dilation on RV function. Our results suggest that RV dilation per se may be more important than the type of lesion, timing of intervention or whether TR or PR drives the volume overload in terms of exercise tolerance and RVEF.

We chose RVEDVi as the main matching parameter as it has been proposed as a major criterion to decide on timing of PVR.[4-8] This may however explain why RV function was comparable between groups, as the matching variable is closely associated with the 'outcome' parameter (i.e. possible "overmatching"). However, as detailed above, this criterion is widely used and used in previous clinical trials addressing RV remodeling.[18] It is important to emphasize that our study was not designed to evaluate the impact of PR on RV remodeling in non-ToF vs. rToF; but rather to compare the clinical response and myocardial function at similar RV volumes, because this parameter is commonly used in clinical practice to determine the need for PVR. While our study was not intended to predict the RV response to PVR, our results provide some insight into how PR affects RV function in rToF vs. non-ToF, and consequently whether similar criteria for PVR may be applicable to these different populations. The pediatric age-range, along with their large RV volumes, suggests that RV dilation in both groups occurs relatively early in the clinical course.

RV dilatation in non-TOF

Most of the recent data published in children and young adults after intervention for isolated PS, predominantly

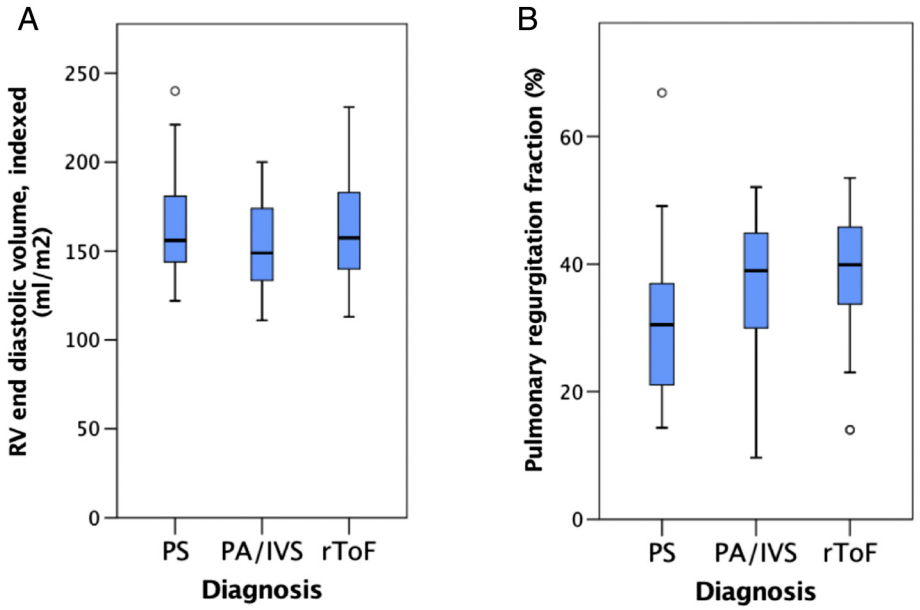
Figure 1



Scatter plots of indexed RV end diastolic volume (RVEDVi) versus RV ejection fraction (RVEF, A and B), RVEDVi versus RV fractional area change (RV FAC, C and D) and ECG QRS duration (in ms) versus RV ejection fraction (RVEF%, E and F), according to groups (Non-ToF vs rToF).No significant differences were observed in Pearson correlation coefficients between non-ToF and rToF groups (RVEF r = –0.39 vs. r = –0.40, Z = 0.04, *P* = .94 and RV FAC: r = –0.45 vs r = –0.40, Z = –0.22 *P* = .83, QRS duration r = –0.77 vs. r = –0.69, Z = –0.62, *P* = .54, respectively).

include patients with mild PR and/or RV dilation.[9-12] Mercer-Rosa et al showed better RV function in patients with isolated PS after valvuloplasty compared with rToF and chronic PR, but their median RVEDVi of 87 ml/m^2 was well below values currently proposed for PVR.[11] In contrast, in our cohort, 40% of non-ToF patients had RV volumes >150 ml/m^2, the lowest cut-off RVEDVi value currently proposed in the literature.[4,8] Discrepant results are also seen in adults when comparing PS vs. rToF patients.[13-15] Zdradzinski et al and Joynt et al independently compared PS patients after PV surgical valvotomy with rToF with similar PR and RVEDVi.[13,14] In those

Figure 2



Boxplots of cardiac magnetic resonance imaging parameters: Indexed right ventricular end diastolic volume (RVEDVi, A) pulmonary regurgitation fraction (PRF, B) according to diagnosis.PS, Pulmonary stenosis; PA/IVS, Pulmonary atresia with intact ventricular septum; rToF, repaired tetralogy of Fallot.

studies, RV and LVEF were higher in PS patients compared with rToF. In contrast, and consistent with our results, Bokma et al found comparable RV and LVEF between the groups when matched by RVEDVi.[15] Although our study included PA/IVS patients who may have myocardial, tricuspid valve and coronary artery abnormalities,[25,26] results were unchanged when excluding this sub-group from the analysis.

Differences between non-TOF and rTOF

Patients with non-TOF versus rTOF differ in factors such as age at and type of intervention to relieve RVOTO, electro-mechanical dyssynchrony (QRS width and RBBB morphology) and prevalence of TR, all of which can influence RV dilation and function.[27-29] The rToF group trended to have more severe PR. It may be that although PR is less in non-ToF patients, they overall have more TR; and thus, comparable volume loading and RVEDVi.

Although peak VO_2 was similar between the groups, endurance time and % predicted peak workload were different. Given the relatively small sample size, we cannot completely exclude the possibility that the study was underpowered to detect a true difference in exercise capacity.

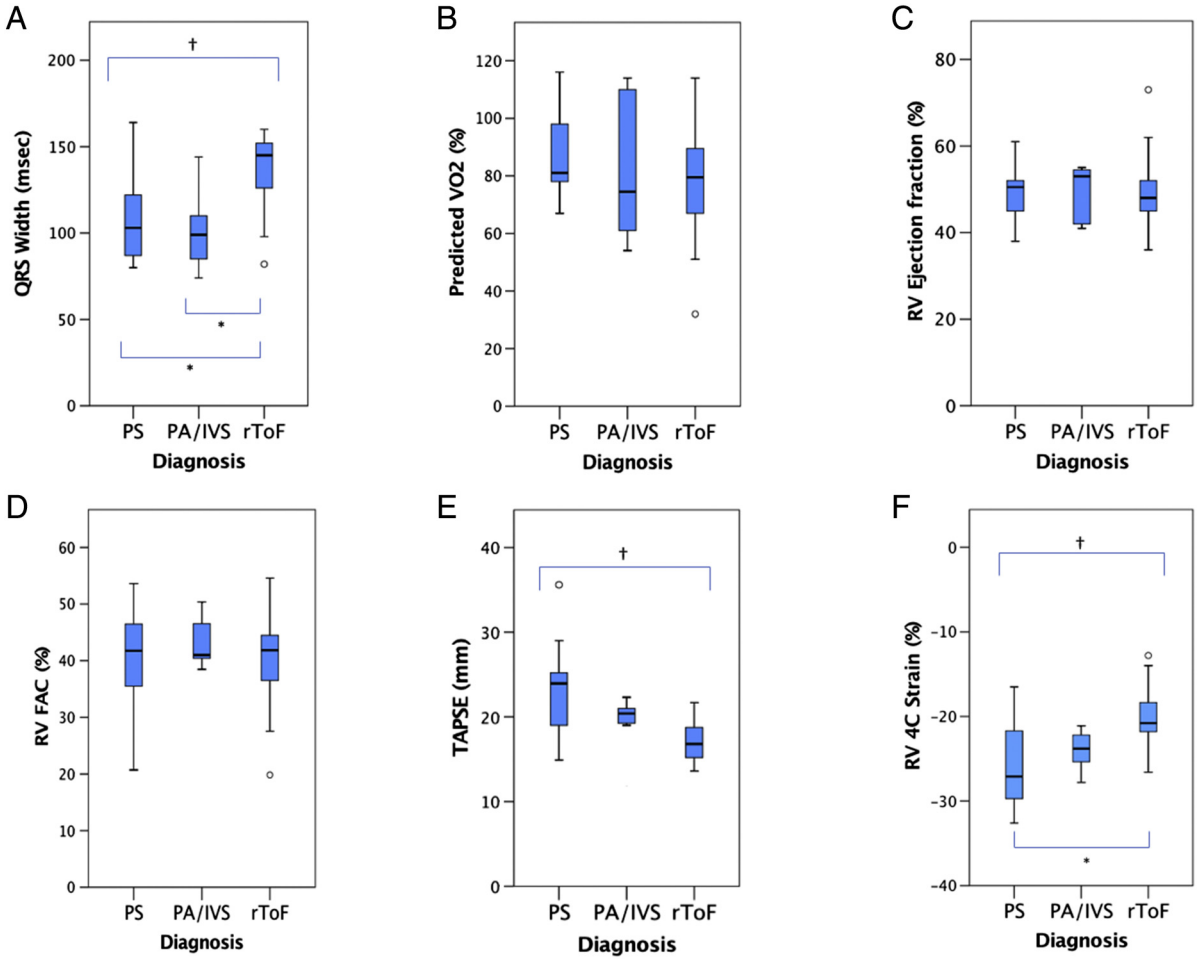
Despite the similar global RV function, assessed by echocardiography (RV FAC) or CMR (RVEF), a consistent significant reduction in longitudinal and regional RV function (TAPSE, TDI S′ and lateral wall and 4C-RV strain) was seen in rToF vs. non-ToF patients. This implies that although global RV function was similar between groups, there are nonetheless different pathophysiological substrates between these conditions, which may be related to surgical intervention in the rToF group, including ventricular septal defect and transannular patches, dyssynchrony and fibrosis that ultimately affect cardiac mechanics and in the longer-term, RV remodeling.[4,27] Another explanation could be the lack of assessment of the RVOT region where the more frequent transannular patch in the rToF group could be related with the observed difference, but the lack of difference between FAC (that does not include the RVOT) and the RVEF do not support this hypothesis.

While not the focus of the current study, RVEDVi and RVEF were associated with QRS duration. QRS duration and RBBB morphology lead to RV electro-mechanical dyssynchrony, dysfunction and may worsen clinical prognosis in rToF.[4,28,30] In the current study, the non-ToF group had a shorter QRS duration and less frequent RBBB than rToF and while global RV function was similar between the groups, there was a significant correlation of QRS width and RVEF. This suggests that QRS duration correlates with dysfunction and may be a long-term risk-factor in both groups as we have recently shown in detail in patients with rTOF.[30]

Limitations

This retrospective study has limitations including a relatively small sample size, variability in the presence

Figure 3



Boxplots of QRS width (A), predicted VO_2 max (B), right ventricular ejection fraction by cardiac magnetic resonance imaging (RV EF, C) and echocardiographic parameters of global (D: RV FAC) and longitudinal RV function (E: TAPSE and F: RV 4C Strain) according to diagnosis.PS, Pulmonary stenosis; PA/IVS, Pulmonary atresia with intact ventricular septum; rToF, Repaired Tetralogy of Fallot. †$P < .05$ between subgroup means as determined by one-way ANOVA. *$P < .05$ between the specific subgroups indicated by the bracket as determined by post hoc Bonferroni test.

and timing of CMR and exercise testing and incomplete data in some patients. To reduce bias, when data was missing in a subject, we excluded that data from the matched control. As detailed above, we included patients with pulmonary atresia in both groups, entities with known clinicopathological differences compared with isolated PS or ToF and PS, and potential different approaches in the initial management. Nevertheless, the PA/IVS and ToF/ PA patients had similar PR and had comparable RV volumes to those patients with isolated PS or ToF PS. Thus, these patients present similar clinical problems and considerations relevant to the aims of this study and were included. We further performed detailed sub-group analysis of these patients and the results were similar.

The cross-sectional design of this study does not allow assessment of the rate of progression of RV dilation and dysfunction, and the response to PVR between the groups. These are both important topics which warrant additional study. Our results cannot be automatically extrapolated to non-ToF patients without significant RV dilation where some studies have shown that these patients have better RV function compared to rToF.[11] Arrhythmia and sudden death are uncommon in our pediatric population and we could not adequately assess these important outcomes.

Conclusion

In conclusion, when matched by RV volume, global RV function and exercise capacity are similarly reduced in

non-ToF and rToF patients with clinically important PR and RV dilation. This suggests that PR and RV dilation, rather than the intrinsic disease, underlies global RV dysfunction. However, at the same time, our results suggest that further study is needed to assess the causes for, and long-term consequences of, differences in regional and longitudinal function in non-ToF versus rTOF patients as this may affect their management, and the impact of PVR in a longitudinal study.

Acknowledgements

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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