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ORIGINAL ARTICLE

The Impact of the Right Ventricular Outflow Tract Patch on Right Ventricular Strain in Tetralogy of Fallot: A Comparison with Valvar Pulmonary Stenosis Utilizing Cardiac Magnetic Resonance

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Abstract A non-contractile transannular patch (TAP) in the right ventricular outflow tract (RVOT) contributes to ventricular dysfunction after tetralogy of Fallot (TOF) repair. We compared regional right ventricular (RV) strain in repaired TOF with valvar pulmonary stenosis (VPS) after balloon valvuloplasty to investigate the effects of TAP. Retrospective review of 26 cardiac magnetic resonance studies of TOF ($n=13$) and VPS ($n=13$) subjects matched by degree and duration of pulmonary regurgitation (PR). Feature tracking strain analysis was performed. Student's t tests, Pearson correlation, and linear regression were applied. RV ejection fraction (EF) was normal and similar between TOF and VPS (60 and 65%, respectively, $p=0.8$). RV 4-chamber Lagrangian longitudinal strain (RV 4ch LS) was worse in both groups compared to normals but comparable to each other: −18.2 (95% CI −3.6 to −33) for TOF and −20.2 (95% CI −12.4 to −28) for VPS, $p=0.5$. RVOT LS was worse than RV 4ch LS in TOF, $p=0.05$, but not in VPS, $p=0.19$. There were no significant differences in RVOT strain between groups, $p=0.18$. RVOT strain and RV 4ch LS correlated positively with RV EF in VPS ($r=0.72$, $p=0.003$ and $r=0.55$, $p=0.04$). PR degree correlated negatively with RVOT LS for TOF and VPS. Longitudinal strain is diminished in VPS and TOF subjects with preserved RV EF. TAP could explain worse RVOT strain in TOF. Longitudinal studies are needed to ascertain if RV strain predicts worsening of RV EF.

Keywords Cardiac MRI · Strain · RV function · Congenital heart disease

Abbreviations

PR	Pulmonary regurgitation
TOF	Tetralogy of Fallot
RV	Right ventricle
TAP	Transannular patch
RVOT	Right ventricular outflow tract
VPS	Valvar pulmonary stenosis
CMR	Cardiac magnetic resonance
PR	Pulmonary regurgitation
FTS	Feature tracking strain
4ch	4-chamber
LS	Longitudinal strain
EF	Ejection fraction
SSFP	Steady-state free-precession
ESV	End-systolic volume
EDV	End-diastolic volume
RF	Regurgitant fraction
CPA	Cardiac performance analysis
HARP	Harmonic phase
BSA	Body surface area
LGE	Late gadolinium enhancement
SPAMM	Spatial modulation of magnetization

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Introduction

Outcomes in tetralogy of Fallot (TOF) are in part determined by residual pulmonary regurgitation (PR) following repair, usually with placement of a transannular and/or right ventricular outflow tract (RVOT) patch. With time, PR results in right ventricular (RV) dilation and eventually ventricular dysfunction in many patients. A non-contractile patch in the RV outflow tract has been associated with RV systolic dysfunction [1] although specific effects of the RVOT patch on regional RV function have not been completely defined. 2D strain analysis by cardiac magnetic resonance (CMR) is a robust technique for evaluating regional cardiac function [2]. We aimed to characterize regional RV systolic function using feature tracking strain analysis (FTS) by comparing patients with repaired TOF and RVOT patch to patients with valvar pulmonary stenosis (VPS) after balloon dilation valvuloplasty, who do not have RVOT patches. We hypothesized that even after matching for duration and severity of PR, there would be differences in regional function between the two groups that might be related to the presence of an RVOT patch.

Materials and Methods

This study was approved by The Children's Hospital of Philadelphia Institutional Review Board for the Protection of Human Subjects.

Study Population

Subjects 8–18 years with surgically repaired TOF or VPS after balloon valvuloplasty were identified. These subjects had previously participated in a cross-sectional study for whom protocol-based CMRs were available and had provided informed consent at enrollment [3, 4]. Subjects were matched by duration and severity of PR using propensity scores. Severity of PR was defined by regurgitant fraction (RF) and considered mild if ≤20%, moderate if 20–40%, and severe if >40%. Duration of PR was defined as the time (years) between initial procedure (complete repair for TOF or balloon valvuloplasty for VPS) and CMR. Residual RVOT obstruction may have an effect on strain; thus, subjects with RVOT peak velocity >2 m/sec were excluded.

CMR: CMR studies were performed as part of a study protocol on a Siemens 1.5-Tesla Avanto Whole-Body Magnetic Resonance system (Siemens Medical Solutions, Malvern, Pennsylvania) using a standardized protocol, previously published by our group (Table 1) [5]. Balanced steady-state free-precession (SSFP) cine CMR acquisitions were obtained in 4-chamber and long-axis planes and contiguous short-axis cine imaging from the atrioventricular junction through the cardiac apex. A cine SSFP sequence in the short-axis view was used (TE/TR 2.0/45 ms; flip angle 75°–90°; matrix size 196×196) to assess ventricular end-systolic and end-diastolic volumes (ESV, EDV). The RV infundibulum was included in the RV volume up to the pulmonary annulus. Balanced SSFP cines were analyzed using standard Siemens analysis software (Argus) for ventricular volumes and function. RV ejection fraction (EF) was calculated as $[(EDV - ESV)/EDV] \times 100$ (in %). Phase-contrast velocity mapping with a flow-sensitive, gradient-echo sequence was performed in the main pulmonary artery to assess the RF. CMR variables included RVEF, RV EDV, and RV ESV, and pulmonary RF. For RV volumetric calculations, the endocardial contour included the RVOT region. Trabeculations were included within the RV cavity. All volumes were indexed to body surface area, and corresponding *z*-scores were calculated using published normative data [6, 7].

RV Strain Measurements on CMR

Feature tracking strain analysis of SSFP cines was performed on the RV in 4-chamber long axis (4ch) and sagittal RVOT views to yield RV 4ch LS and RVOT LS (Fig. 1 and Online Supplemental Video 1). Strain measurements were performed with 2D Cardiac Performance Analysis (TomTec 2D CPA, v1.0, Munich, Germany). 2D CPA is a vector-based method that performs strain analysis via feature tracking techniques, as previously described [8]. A contour was applied by a single trained reader (SA) along the RV endocardial border, and the software automatically propagated the contour by following its features through the remainder of the cardiac cycle. The 4ch RV contour

Table 1 CMR protocol

Technique	Purpose
Cine SSFP images of LV 2-chamber long axis, RV 2-chamber long axis, and 4-chamber long axis	Visualize LV, RV, and 4-chamber long axis and set up ventricular short-axis stack
Cine SSFP stack of contiguous short-axis images	Assess ventricular volumes and function
Cine SSFP image of RV and RV outflow tract (RVOT) in sagittal plane	Visualize RV, RVOT

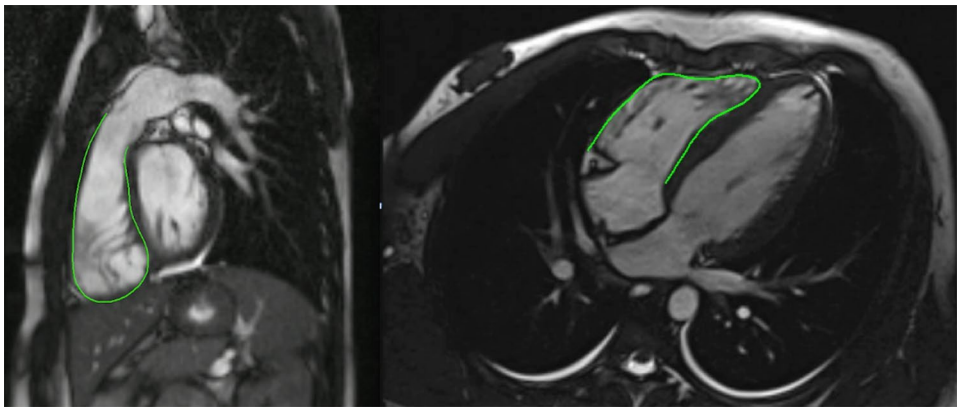

Fig. 1 Feature tracking analysis of the right ventricle contours applied to the RV in sagittal RVOT and apical 4-chamber views

included the RV free wall and ventricular septum. The tracing was visually inspected to ensure adequate tracking. Studies with poor tracking of the endocardium were excluded. The FTS software-derived parameters of ventricular function including strain, strain rate, tissue velocity, and displacement. Validation of this analysis system has been previously reported against harmonic phase tagged MRI [8]. By convention, longitudinal strain is expressed as a negative value; therefore, a higher negative number indicates greater LS and therefore better systolic function. Normal longitudinal strain was defined as $>-29\%$ in the RV 4ch view [9]. Strain at the RVOT was derived to perform comparisons between groups. To our knowledge, normal values for RVOT strain have not been defined in the literature.

Statistical Analysis

Variables are presented as mean, and categorical variables as counts (percentages). The data were normally distributed; thus, two-tailed paired Student's *t* tests were applied to evaluate differences between groups. Pearson correlation was used to assess relationships between variables. The absolute value of RV strain was used to compare the magnitude of strain to PR, RV volumes, and RV EF. Statistical significance was reached for p values <0.05. Statistical analyses were performed using Stata 11.2 (Stata Corporation, College Station, Texas).

Results

Demographics, Pulmonary Regurgitation, RV Volume, and Ejection Fraction

There were 26 subjects in the study: 13 matched pairs of TOF and VPS. There were no significant differences between the TOF and VPS groups in age, body surface area (BSA), RV volumes (indexed to BSA), and RV ejection fraction (Table 2). By study design, duration and severity of PR were comparable between the two groups. RV ejection fraction was normal in both groups (Table 2).

Table 2 Tetralogy of Fallot versus valvar pulmonary stenosis

	Tetralogy of Fallot $n=13$	Valvar pulmonary stenosis $n=13$	TOF versus VPS p value
Mean age at CMR (years)	14.5 (± 2.5)	15.2 (± 3.6)	0.57
Mean body surface area (BSA) (m^2)	1.5 (± 0.24)	1.7 (± 0.5)	0.23
Mean pulmonary valve regurgitant fraction (%)	20.3 (± 14.1)	18 (± 11.5)	0.84
Mean duration of pulmonary regurgitation from pulmonary valve operation/procedure (years)	14.2 (± 2.5)	14 (± 4)	1
Mean RV end-diastolic volume indexed to BSA (ml/m^2)	106 (± 27.2)	95 (± 29.8)	0.34
Mean RV end-systolic volume indexed to BSA (ml/m^2)	43 (± 18.6)	34 (± 16.6)	0.21
Mean RV Ejection Fraction (%)	60.3 (± 8.7)	65 (± 7.5)	0.15
Mean RV 4ch longitudinal strain	−18.2 (± 7.3)	−20.2 (± 3.9)	0.49
Mean RVOT longitudinal strain	−14.1 (± 7.4)	−17.9 (-± 5.4)	0.18

Results are expressed as mean (± standard deviation)

Table 3 Within group analysis

	RV 4ch longitudinal strain (mean)	RVOT longitudinal strain (mean)	*p* value
Tetralogy of Fallot	−18.2 (± 7.3)	−14.1 (± 7.4)	0.05
Valvar pulmonary stenosis	−20.2 (± 3.9)	−18.2 (± 5.4)	0.19

Results are expressed as mean (± standard deviation)

Table 4 Correlations between RV longitudinal strain (absolute) and pulmonary regurgitation, RV volumes, and RV ejection fraction

	TOF (*r*)	*p* value	VPS (*r*)	*p* value
Pulmonary regurgitant fraction				
RV 4ch LS	−0.12	0.68	−0.31	0.29
RVOT LS	−0.55	0.04	−0.58	0.03
Indexed RV end-diastolic volume				
RV 4ch LS	−0.13	0.66	−0.34	0.23
RVOT LS	−0.44	0.12	−0.52	0.06
Indexed RV end-systolic volume				
RV 4ch LS	−0.23	0.43	−0.42	0.13
RVOT LS	−0.52	0.07	−0.59	0.03
RV ejection fraction				
RV 4ch LS	0.35	0.22	0.55	0.04
RVOT LS	0.53	0.06	0.72	0.003

4ch and RVOT LS denotes 4-chamber and right ventricular outflow tract longitudinal strain, respectively

Region-Specific RV Strain

RV LS from the 4-chamber view (RV 4ch LS) was diminished in the TOF and VPS groups compared to published normals (Table 2) [9]. There was no significant difference in RVOT or RV 4ch LS in the TOF group as compared to the VPS group (Table 2). Strain at the RVOT was worse than RV 4ch LS in the TOF group, $p = 0.05$. In contrast, there was no difference between RVOT and RV 4ch LS in the VPS group, $p = 0.19$ (Table 3).

Associations of RV Strain with Severity of PR, RV Volumes, and RV Function

Severity of PR:We found a moderate negative correlation between RVOT LS and severity of PR (as quantified by regurgitant fraction) in both groups, suggesting that RVOT strain is worse with more severe PR (Table 4; Fig. 2).

Indexed RV Volumes: Absolute RVOT LS had a moderate negative correlation with indexed RV end-systolic volume in the VPS group ($p = 0.03$). A similar trend was noted in TOF although this did not reach statistical significance (Table 4; Fig. 3). There were no significant relationships between RVOT strain and indexed end-diastolic volumes.

RV Ejection Fraction:For the VPS group, the absolute RVOT strain had a strong positive correlation with RV EF and the 4ch LS had a moderate correlation with RVEF. These associations were not significant in the TOF group (Table 4; Fig. 4).

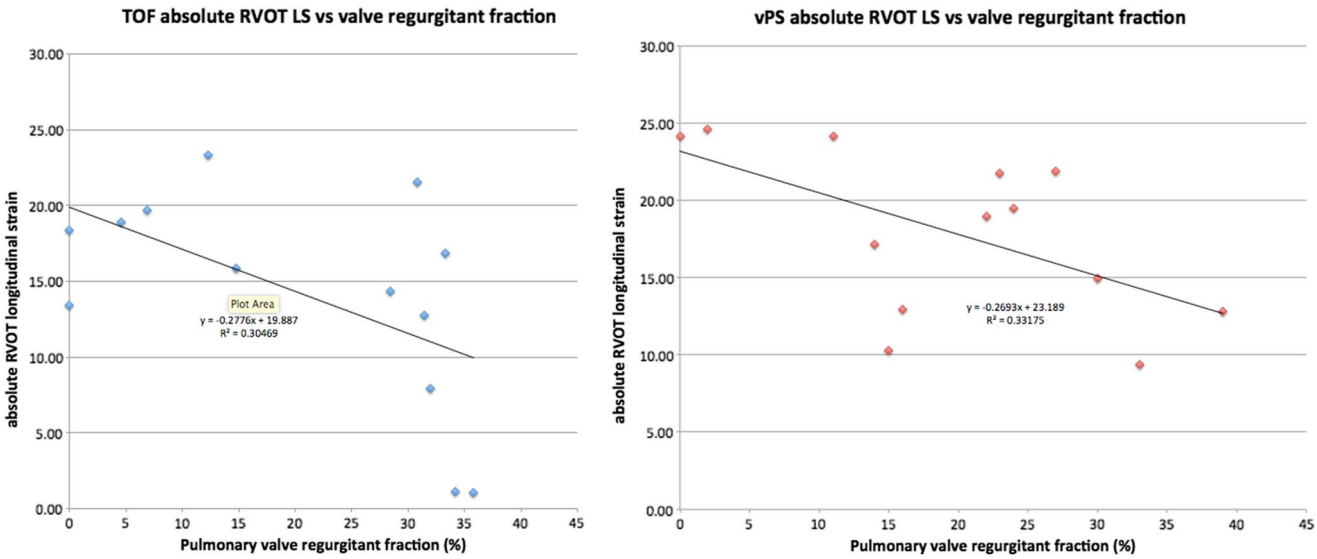

Fig. 2 Linear regression of absolute longitudinal strain at the right ventricular outflow tract (RVOT LS) versus pulmonary valve regurgitant reaction (RF) Tetralogy of Fallot (*left panel*) and valvar pulmonary stenosis (*right panel*). There is a negative correlation between pulmonary valve RF and RVOT LS, $r = -0.55$ ($p = 0.04$) in TOF and $r = -0.57$ ($p = 0.03$) in VPS

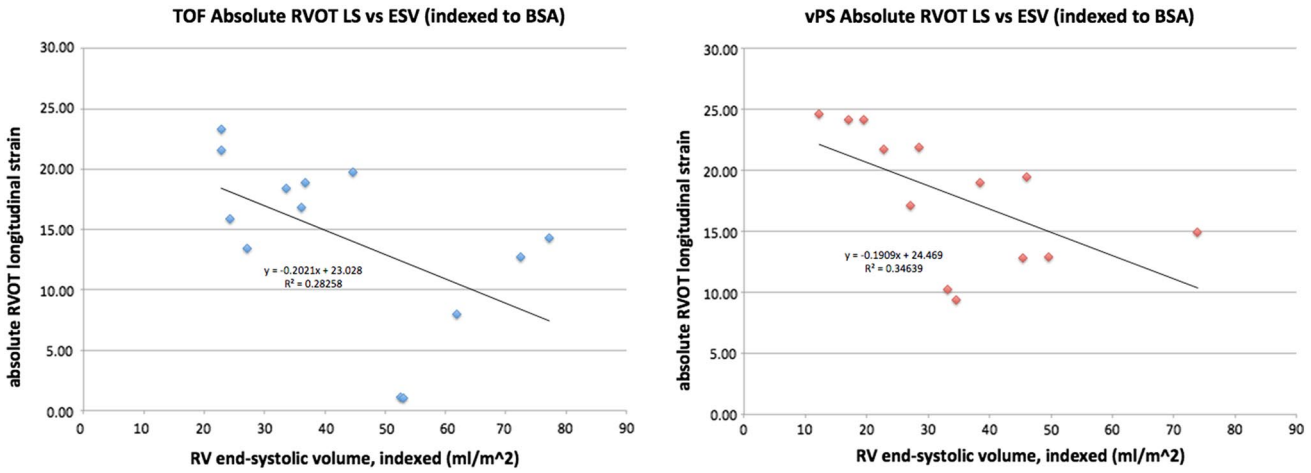

Fig. 3 Linear regression of absolute longitudinal strain at the right ventricular outflow tract (RVOT LS) versus RV end-systolic volume (indexed to BSA) Tetralogy of Fallot (*left panel*) and valvar pulmonary stenosis (*right panel*). There is a negative correlation between RV ESVi and RVOT LS, $r=-0.53$ ($p=0.05$) in TOF and $r=-0.58$ ($p=0.03$) in VPS

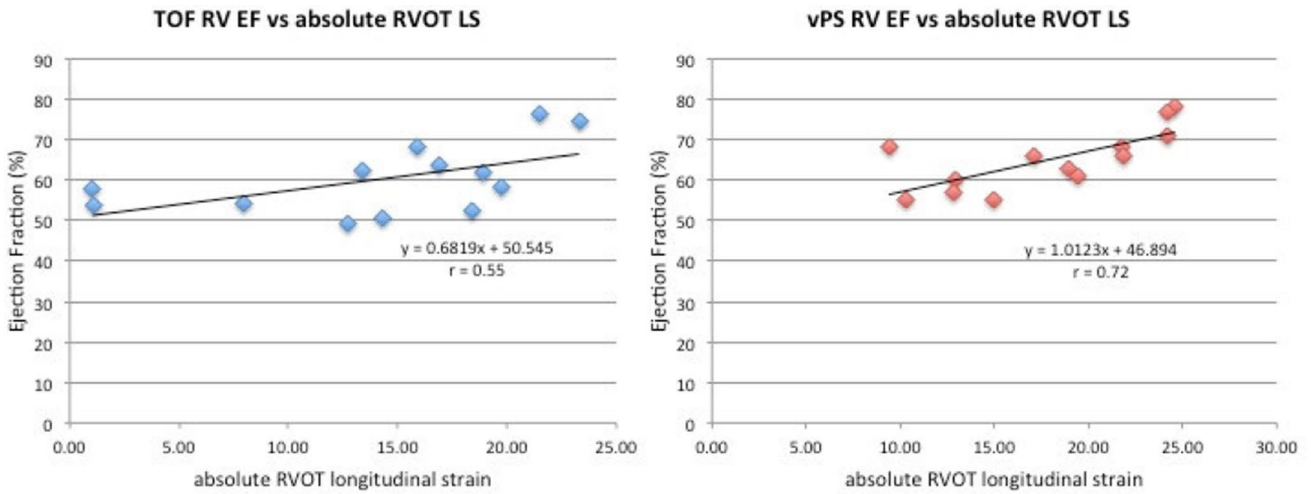

Fig. 4 Linear regression of RV ejection fraction (EF) versus absolute longitudinal strain at the right ventricular outflow tract (RVOT LS) Tetralogy of Fallot (*left panel*) and valvar pulmonary stenosis (*right panel*). There is a positive correlation between RV EF and RVOT LS in VPS $r=0.72$ ($p=0.003$) but not in TOF $r=0.55$ ($p=0.06$)

Discussion

The goal of this study was to evaluate right ventricular systolic function and in particular to assess the right ventricular outflow tract (RVOT), in an attempt to evaluate the contribution of the RVOT patch to RV function in patients with Tetralogy of Fallot following repair. Specifically, the hypothesis was that patients with an RVOT patch would have worse systolic function quantified by strain as compared to patients with valvar pulmonary stenosis treated with a catheter-based intervention and therefore without an RVOT patch. Our study did not find a difference in strain in the RVOT in the two groups. At the same time, the study did find that in the TOF group, RVOT strain is worse compared to other regions in the RV, which did not occur in the VPS group.

Reduced RV function in TOF patients has been reported in several studies [10–14], and RV volumes and function stand out as the strongest independent factors associated with clinical outcome [15, 16]. Orwat et al. recently reported that RV strain measured on cardiac MRI using the FTS method was an independent predictor of clinical outcome in TOF patients [17]. In our study, RV strain was reduced in both the TOF and VPS groups, whereas ejection fraction by conventional CMR measurements was normal. This finding suggests that even mild PR can be associated

with RV dysfunction measured by strain. While TOF as a group is well recognized to have RV dysfunction, it is noteworthy that VPS patients with mild residual PR and preserved EF may have subtle abnormalities in RV function as detected by strain. These findings suggest that both groups should be followed with measures that are more sensitive to detect abnormalities in function than ejection fraction. It is possible that strain could serve as an early indicator of dysfunction given that it is abnormal prior to overt changes in ejection fraction [18–21]. Similar to our results, Luijnenburg et al. studied patients with valvar pulmonary stenosis and TOF and reported comparable RV ejection fractions between the two groups, even though the TOF group had more severe pulmonary regurgitation and more dilated right ventricles [1]. This finding suggests that their pump function is comparable, but does not provide information on contractility, since ejection fraction does not identify the abnormal myocardial mechanics that may exist between different pathological states affecting the RV. Puranik et al. previously reported significantly diminished RV systolic function (by EF) and larger end-systolic volumes in TOF subjects compared to VPS [22] and postulated that patients with a non-contractile RVOT have reduced overall RV function compared to those with contractile RVOTs. We demonstrate that strain can be diminished in the RVOT in comparison to the rest of the RV in TOF patients. This suggests that strain may be reported as a complementary parameter of function in the assessment of RV systolic function in this patient population.

In this study, strain was reduced at the RVOT as compared to 4ch longitudinal strain which did not include the RVOT in the TOF group. This is likely due to the presence of a non-contractile (and sometimes aneurysmal) RVOT patch in patients with TOF. Prior studies have also reported diminished RVOT function in the TOF population using different techniques [23]. RVOT fibrosis appears to contribute to RVOT dysfunction, which in turn is associated with overall RV dysfunction [24, 25]. These studies suggest that the RVOT patch has a negative impact on overall ventricular function and therefore inform our understanding of regional RV dysfunction. RVOT fibrosis and dysfunction have been specifically linked to clinical outcomes in patients following TOF repair. Babu-Narayan et al. reported late gadolinium enhancement (LGE) indicating fibrosis or scar at surgical sites in the RVOT in 99% of patients following TOF repair. Patients with increased fibrosis or scarring had increased biomarkers of myocardial stretch, exercise intolerance, and RV dysfunction [24]. Wald et al. reported that RVOT dyskinesis and higher LGE score correlated significantly with worse RV EF and lower aerobic exercise capacity [25].

Worse RVOT strain was associated with greater pulmonary regurgitation in both the TOF and VPS groups. A similar finding was reported in asymptomatic children after TOF repair, although the study did not examine differences in RVOT strain [26]. Reduced RVOT strain was associated with greater PR in both TOF and VPS groups. It is possible that PR has a negative impact in the contractile properties of the RVOT even in patients without an RVOT patch, or alternatively, worse PR is a reflection of disease severity and therefore is associated with worse RVOT strain. Further study is needed to corroborate this idea.

Finally, this study demonstrates a useful application of feature tracking strain, a technique that can be used in patients with congenital heart disease without adding to the length of the MRI study. FTS has been validated against grid-tagging (spatial modulation of magnetization, SPAMM), the current gold-standard for non-invasive strain assessment [8]. From a technical standpoint, FTS can analyze the thin-walled RV, which has been challenging with SPAMM, and has the potential for widespread application in a number of right-heart disease states. One of the potential benefits of FTS could be the ability to identify subclinical dysfunction in patients with preserved ejection fraction, which has been demonstrated in other disease states, such as cardiomyopathy following exposure to cardio toxic agents [18–21]. Sensitive detection of subclinical dysfunction may become particularly useful in the longitudinal follow-up of patients with repaired TOF, VPS as well as in other forms of congenital and acquired heart disease.

Conclusions and Limitations

We studied a relatively healthy population with mild PR and preserved EF with a small sample size. In particular, the difference in RVOT and 4ch longitudinal strain in the TOF group barely reached statistical significance. However, our findings are of interest given the presence of diminished strain in patients with a relatively normal ejection fraction, and could be more pronounced in a larger sample size and/or in patients with more significant PR or decreased RV EF. Although adverse RV–LV interactions have been noted in patients with dysfunctional RVs, this association was not evaluated in this study. A follow-up study could investigate the effects of RV dysfunction on LV strain.

In conclusion, strain is diminished even in the presence of mild pulmonary regurgitation and preserved ejection fraction. If longitudinal studies confirm that abnormal strain predicts a subsequent drop in RV EF in this setting, then strain might become a sensitive tool to detect right ventricular dysfunction premorbidly. Either way, measures of RV strain would appear to be a useful tool with which to assess RV function concurrently with other measurements. Finally, the role of RVOT dysfunction merits further

investigation and longitudinal studies are warranted to further validate its use.

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Compliance with Ethical Standards

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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