

Original Article

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Corresponding author:

George Slim; Email: gslim@ualberta.ca

Comparisons of right ventricular strain between repaired tetralogy of fallot and isolated pulmonary regurgitation

George Slim¹ , Joseph Pagano¹, Kumaradevan Punithakumar², Michelle Noga² and Edythe Tham¹ 

¹Stollery Children's Hospital, Divisions of Pediatric Cardiology and Diagnostic Imaging, University of Alberta, Edmonton, AB, Canada and ²Servier Virtual Cardiac Centre, Mazankowski Alberta Heart Institute and Department of Radiology and Diagnostic Imaging, University of Alberta, Edmonton, AB, Canada

Abstract

Background: Pulmonary regurgitation leading to right ventricular enlargement may occur after repaired tetralogy of Fallot (rTOF) or balloon dilation for pulmonary valve stenosis. Cardiac magnetic resonance imaging (CMR) guidelines to identify the timing of valve replacement in rTOF are not necessarily applicable to isolated pulmonary regurgitation. This study aims to compare deformation parameters of isolated pulmonary regurgitation and rTOF at comparable right ventricular volume loads. **Methods:** Adopting a quantitative retrospective analytic framework, CMR was performed in 44 patients (0–30 years), 22 in each of the isolated pulmonary regurgitation and rTOF study arms, matched for age (± 12 months), and Right ventricular end-diastolic volume z-score (± 1). Right ventricular longitudinal strain/strain rate and circumferential strain/strain rate were measured. Comparisons between groups were analysed using two-tailed *T*-tests and one-way ANOVA. **Results:** Both groups showed predominance of longitudinal over circumferential strain. Circumferential strain was significantly greater in rTOF compared to isolated pulmonary regurgitation (-26.5% versus -22.3% , $p < 0.05$). Longitudinal strain did not differ between groups. The longitudinal:circumferential strain ratio was significantly lower in rTOF compared to isolated pulmonary regurgitation (1.24 versus 1.53, $p = 0.05$). Circumferential and longitudinal strain rates did not differ between groups. **Conclusions:** The right ventricles in rTOF demonstrate greater reliance on circumferential strain in response to increased volumes. The decrease in longitudinal:circumferential strain ratio suggests rTOF right ventricles display a greater adaptive response to the volume load than isolated pulmonary regurgitation, highlighting the importance of the relative contributions of both circumferential and longitudinal strain in order to understand the mechanisms of right ventricular dysfunction in pulmonary regurgitation.

Background

Pulmonary regurgitation is most frequently encountered after surgical repair for tetralogy of Fallot (TOF),¹ but also occurs in 27% of children up to 14 years after pulmonary valvuloplasty for valvar pulmonary stenosis.² Chronic pulmonary regurgitation leads to progressive enlargement and dysfunction of the right ventricle.¹ This complication plays a crucial role in late morbidity and mortality associated with TOF repair.³ While pulmonary regurgitation can be well-tolerated for an extended period after surgery, it may eventually result in progressive exercise intolerance, heart failure, and tachyarrhythmias.⁴ In many cases, re-intervention in the form of pulmonary valve placement becomes necessary.

Recognising the importance of identifying systolic dysfunction before it becomes irreversible, cardiac MRI indicators utilising right ventricular volumes and pulmonary regurgitant fraction for pulmonary valve replacement have been incorporated into guidelines and are commonly used in clinical practice for managing patients with repaired tetralogy of Fallot (rTOF).^{3,5,6} In contrast to pulmonary regurgitation following TOF repair, isolated pulmonary regurgitation in an otherwise normal heart is generally well-tolerated for decades, with symptoms potentially not manifesting for up to 40 years.⁴

The progressive right ventricular volume load in rTOF results in reduced exercise capacity and an increased risk of ventricular arrhythmias with a potential risk of sudden death. Ventricular dysfunction is a crucial predictor of poor long-term outcomes. Among these risk factors, both left and right ventricular systolic dysfunction have been independently associated with worse outcomes, including sudden cardiac death.⁴ Nevertheless, right ventricular volumes and ejection fraction, which are traditionally used for these indications, have limitations due to their dependence on loading conditions and their inability to fully reflect contractile function.^{7,8}

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Indications for pulmonary valve replacement in isolated pulmonary regurgitation have not been established.⁹ The key distinction lies in the absence of prior bypass surgery or intracardiac repair. The primary objective of this study is to investigate whether isolated pulmonary regurgitation and rTOF exhibit similar functional parameters at comparable right ventricular volumes. Our hypothesis is that strain patterns, specifically longitudinal versus circumferential strains, will exhibit significant differences at comparable right ventricular volumes. Understanding whether the functional parameters of isolated pulmonary regurgitation are maintained at the same volume load compared to rTOF patients is vital to determining if different guideline parameters should be adopted for pulmonary valve replacement in isolated pulmonary regurgitation.

Study objective

To compare deformation parameters between isolated pulmonary regurgitation with rTOF patients.

Methods

Study population

Inclusion criteria encompassed individuals aged <30 years who had undergone cardiac MRI to assess right ventricular volume, function, and regurgitant fraction as part of the routine evaluation for pulmonary regurgitation. For patients with multiple cardiac MRI studies, the most recent one was selected. Patients were excluded from the study if they had significant metallic artefacts that compromised image quality, such as those from prosthetic valves, stents, or surgical clips, as these could interfere with accurate image interpretation and strain analysis. In addition, poor-quality cine data that hindered reliable right ventricular strain tracking, whether due to motion artefacts, low signal-to-noise ratio, or inadequate endocardial border definition, led to exclusion. Studies with missing or incomplete imaging sequences required for comprehensive ventricular assessment were also omitted to maintain data integrity. Furthermore, patients with associated complex congenital or acquired cardiac defects beyond the primary study inclusion criteria were excluded to minimise confounding variables and ensure a more homogeneous comparison between groups. These exclusion criteria were established to uphold high imaging quality, enhance the accuracy of strain analysis, and reduce variability within the study population.

The cardiac MRI database was reviewed for all patients with rTOF and resultant pulmonary regurgitation or isolated pulmonary regurgitation after balloon dilation for pulmonary valve stenosis. Upon reviewing a total of 154 studies meeting inclusion criteria, a total of 44 patients (22 in each group) were manually matched 1:1 for age (± 12 months) and right ventricular end-diastolic volume z-score (± 1) (Table 1).

Data collection

Patient characteristics including diagnosis, type of surgical repair, age at TOF repair or balloon pulmonary valvuloplasty, age at the time of MRI, gender, weight, height, and body surface area were obtained. Cardiac MRI images were acquired utilising a Siemens 1.5 T Magnetom Aera (Siemens Healthcare, Erlangen, Germany) equipped with a 32-channel body array coil with end-expiratory breath-holds. Standard balanced steady-state free precession cines were obtained to evaluate the anatomy and volumetric function

Table 1. Group comparisons of clinical, volumetric, functional, and ventricular deformation

	iPR	rTOF	SD	p-value
Age (years) at time of CMR study	16.45	16.49	4.2	>0.05
Age (years) at time of repair/intervention	1.18	0.64	2.06	>0.05
BSA (m ²)	1.61	1.59	0.32	>0.05
Pulmonary RF (%)	31.62	37.53	0.14	>0.05
Pulmonary RVi	20.09	20.95	11.51	>0.05
RVEF (%)	54	50.28	6.25	>0.05
RVEDVi (ml/m ²)	129	132.47	26.18	>0.05
RVEDV (Z-score)	2.73	2.6	1.74	>0.05
RVESVi (ml/m ²)	70.05	65.89	14.62	>0.05
Peak Longitudinal Strain (%)	-31.89	-31.48	7.85	>0.05
Peak Circumferential Strain (%)	-22.31	-26.52	6.62	0.03
GLS/GCS ratio	1.53	1.24	0.51	0.05

Comparisons of mean clinical, volumetric, functional, global strain, and strain rate values between patient groups. RF = Regurgitant fraction; RVi = Regurgitant volume indexed to BSA; RVEDVi = Right ventricular end-diastolic volume indexed to BSA; RVEF = Right ventricle ejection fraction; RVESVi = Right ventricular end-systolic volume indexed to BSA; GLS = Global Longitudinal Strain; GCS = Global Circumferential Strain.

from a standard short-axis stack. Pulmonary flow was measured using phase-contrast imaging at the level of the main pulmonary artery. Images were analysed using CVI42 software (cmr42, Circle Cardiovascular Imaging, Calgary, Canada) to calculate right ventricular and left ventricular end-diastolic and end-systolic volumes, right ventricular ejection fraction, stroke volume, pulmonary regurgitant fraction, and pulmonary regurgitant volume. Data were indexed to body surface area where appropriate.

Strain analysis

Right ventricular strain was assessed using a locally developed semi-automated segmentation software. This software has been validated by our group, and we have previously shown good inter-observer and intra-observer reproducibility.¹⁰ Anonymized studies were analysed with the observer blinded to the type of lesion. The software computed the strain parameters and generated graphical plots (Figure 3b and 4b). Global longitudinal strain and strain rate were derived from the standard 4-chamber SSFP cine (Figure 3a), while global circumferential strain and strain rate were obtained from the basal short-axis cine slice just below the right ventricular outflow tract (Figure 4a), following previously described techniques. The global longitudinal strain to circumferential strain ratio was calculated to provide insights into the relative strain patterns. As strain is a negative value, a higher negative value indicates better strain or strain rate.¹⁰

Data analysis

Continuous variables were summarised as mean \pm standard deviation or median with interquartile range depending on data normality. Categorical variables were presented as frequency distributions. Comparison of cardiac MRI ventricular volumes, function, and regurgitation parameters among groups utilised two-tailed T-tests. The data were analysed using IBM SPSS Statistics

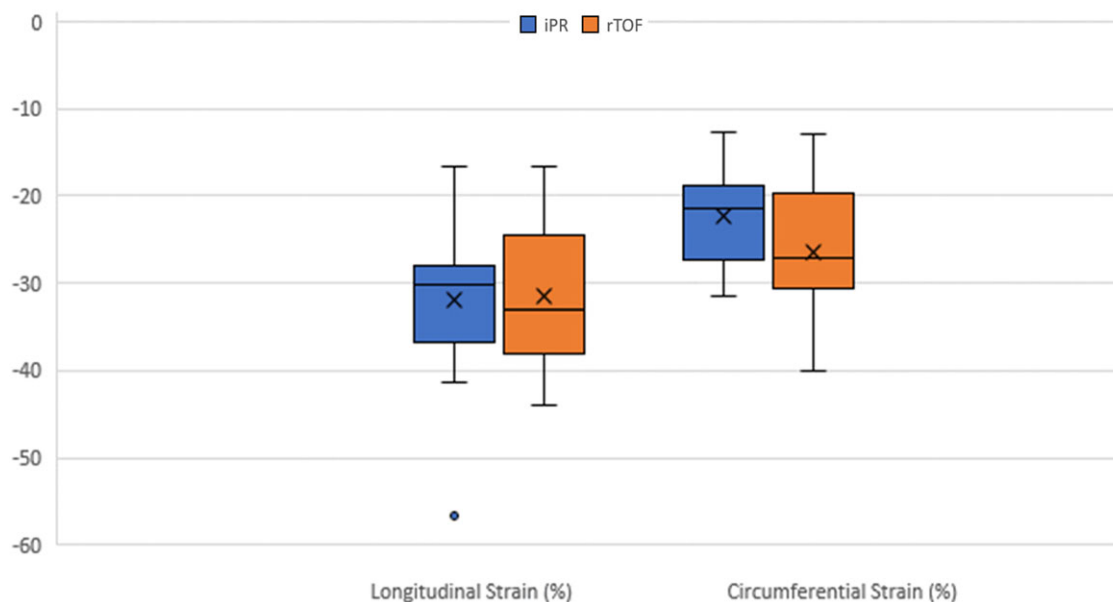


Figure 1. Longitudinal strain vs Circumferential Strain at comparable volumes.

(Version 27). CMR parameters across different patient groups were compared using either one-way ANOVA or the Kruskal–Wallis test, as appropriate, with Tukey or Mann–Whitney tests for post-hoc analysis.

Results

A total of 44 cardiac MRI studies (22 in each group) were included, with 45% males. There were no differences among the clinical characteristics between rTOF and iPR patients including height, weight, gender, and body surface area. ($p > 0.05$) (Table 1). All rTOF patients underwent transannular patch repair resulting in free pulmonary regurgitation, while isolated pulmonary regurgitation patients underwent balloon pulmonary valvuloplasty, most of which (77%) occurred within the first year of life, with the remaining (23%) undergoing balloon valvuloplasty between the ages of 2 and 11 years. No other interventions, aside from the initial transannular patch or balloon pulmonary valvuloplasty, were performed on these patients. Patients who underwent surgical repair of TOF were younger than the age of balloon pulmonary valvuloplasty for pulmonary stenosis, but this was not significantly different. There were no significant differences between their right ventricular volumes, indexed right ventricular volumes, right ventricular ejection fraction, regurgitant fraction, or indexed regurgitant fraction—indicating adequate 1:1 matching (Table 1). Two rTOF patients (4.5%) had mildly reduced right ventricular ejection fraction. Right ventricular ejection fraction was classified as mildly decreased (35–45%), moderately decreased (30–35%), and severely decreased (less than 30%). However, this was not statistically significant when comparing both groups (54% versus 50% in isolated pulmonary regurgitation versus rTOF, respectively) (Table 1). There were no differences in right ventricular volumes, left ventricular volumes, left ventricular ejection fraction, or left ventricular mass index between the two groups (Table 1). There were no statistically significant age or right ventricular end-diastolic volume z-score differences between the matched patients and those excluded in the matching process.

Strain parameters

Both isolated pulmonary regurgitation and rTOF had similar longitudinal strains and showed greater longitudinal strain compared to circumferential strain (Table 1). rTOF patients demonstrated significantly higher circumferential strain (−26.5%) compared to the isolated pulmonary regurgitation group (−22.3%) ($p < 0.05$). (Figure 1). This resulted in a longitudinal:circumferential strain ratio that was lower in rTOF (1.24) compared to isolated pulmonary regurgitation (1.53), just reaching statistical significance ($p = 0.05$). (Figure 2). There were no significant differences between both circumferential and longitudinal strain rates between the isolated pulmonary regurgitation and rTOF groups (circumferential strain rate: −1.1/s versus −1.04/s, $p > 0.05$). (longitudinal strain rate: −1.51/s versus −1.55/s, $p > 0.05$) (Table 1).

Discussion

The findings of this study shed light on the intriguing differences in deformation parameters between patients with rTOF and those with isolated pulmonary regurgitation when confronted with comparable right ventricular volume loads. While there were some similarities in the strain pattern of both isolated pulmonary regurgitation and rTOF, there were also some subtle differences that may reflect the underlying myocardial architecture of each lesion. Echocardiographic strain imaging in TOF has shown the value of deformation parameters as more sensitive markers of systolic function and remodelling after pulmonary valve replacement.^{7,11–13} Cardiac MRI measured strain has been studied in adults with rTOF, but less so in the paediatric population.¹⁴ Our previous study outlined the importance of measuring both longitudinal and circumferential deformation parameters in rTOF and their associations with standard cardiac MRI guideline parameters for pulmonary valve replacement.¹⁰ In our previous study, the control group had significantly smaller ventricular volumes and higher right ventricular ejection fraction (both $p < 0.01$) compared to patients with rTOF.

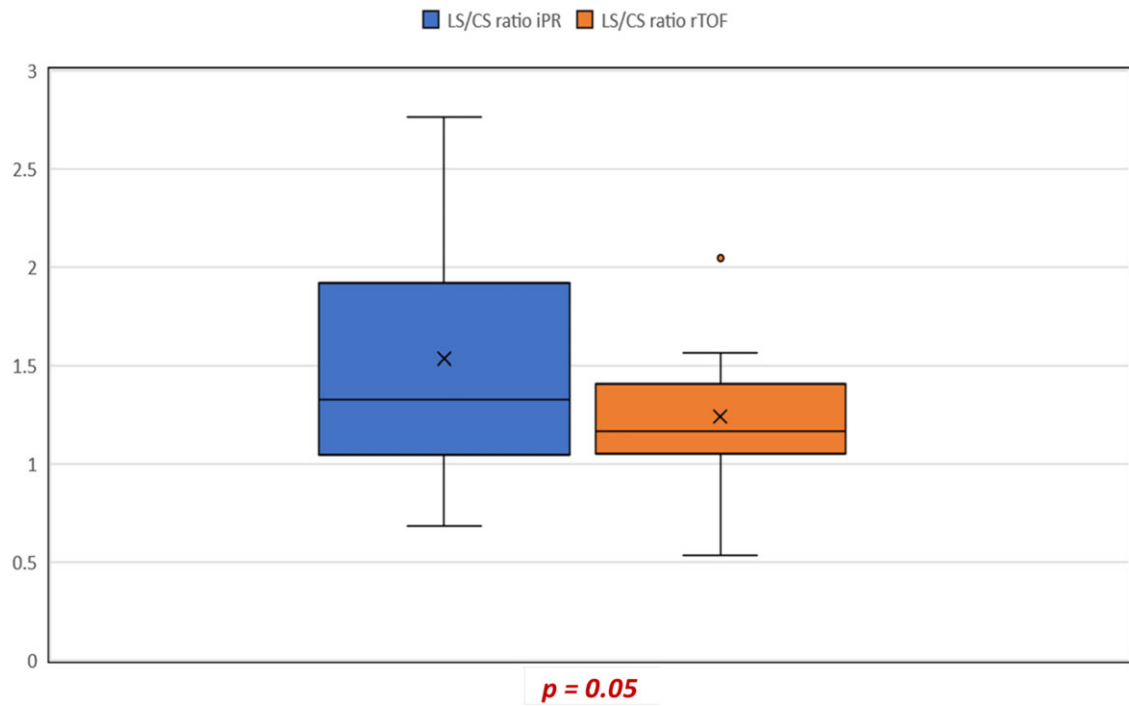


Figure 2. Global longitudinal strain / global circumferential strain—ratio.

Table 2. Prior group comparisons of volumetric, functional, and ventricular deformation¹⁰ (Goot, et al)

	TOF	Controls	p-value
RVEDVi (ml/m2)	152 ± 77.5	78 ± 13.2	<0.0001
RVESVi (ml/m2)	72 ± 47.7	37 ± 8.8	<0.0001
RVEF (%)	51 ± 8.8	54 ± 5.3	<0.0001
Pulmonary RF (%)	37 ± 16		
Longitudinal Strain (%)	−20 ± 3.2	−24 ± 3.1	<0.0001
Longitudinal SR (%/s)	−1 ± 0.2	−1.1 ± 5.3	NS
Circumferential Strain (%)	−17 ± 3.7	−32 ± 3.7	<0.0001
Circumferential SR (%/s)	−1 ± 0.2	−2.2 ± 0.7	<0.0001
Longitudinal/Circumferential Strain (%)	1.2 ± 0.3	0.7 ± 0.3	<0.0001

Comparisons of median volumetric, functional, global strain, and strain rate values between patient groups. RF = Regurgitant fraction; RVEDVi = Right ventricular end-diastolic volume indexed; RVEF = Right ventricle ejection fraction; RVESVi = Right ventricular end-systolic volume indexed; SR = Strain rate.

They also exhibited better global longitudinal and circumferential strain ($p < 0.01$), with a notably greater difference in circumferential strain. While longitudinal strain rate was comparable between groups, the control group had a significantly different circumferential strain rate. Additionally, the longitudinal-to-circumferential strain ratio in controls was significantly different from that of the rTOF group ($p < 0.01$).¹⁰ (see Table 2)

Determining the optimal timing for pulmonary valve replacement in patients with pulmonary regurgitation is a complex task. Recent review articles comprehensively discuss this challenge, with guidelines from various cardiovascular societies providing recommendations with slight differences in the threshold right

ventricular volumes. Generally, pulmonary valve replacement is advised for patients with right ventricular outflow tract dysfunction and symptoms related to it.³ Thresholds based on right ventricular volumes and ejection fraction are proposed for asymptomatic patients, but do not take into account the contractile function of the ventricle. Striking a balance is crucial to avoid overly late interventions, where right ventricular dysfunction may be irreversible, or intervening too early with smaller valve sizes and limited durability of implanted valves, requiring multiple interventions. Guidelines for the rTOF population, which may be extrapolated to the isolated pulmonary regurgitation population, should be used with caution given the lack of supporting data despite similar physiologic effects.

Recent advancements have shown that speckle-tracking ventricular deformation imaging is superior to ejection fraction in detecting early dysfunction in this patient population.^{11,15,16} Studies have demonstrated associations between right ventricular longitudinal strain from echocardiography and ventricular ejection fraction measured via MRI.¹⁷ Furthermore, reduced longitudinal strain in both the right ventricle and left ventricle have been linked to adverse clinical outcomes including mortality and sustained ventricular tachycardia.¹⁵

Feature tracking is an alternative cardiac MRI technique that overcomes the limitations of echocardiography in older patients with restricted acoustic windows that has been validated against speckle-tracking echocardiography.¹⁷ Impaired right ventricular and left ventricular strain measured through Feature Tracking-Cardiac MRI have been shown to correlate with adverse outcomes, such as death or sustained ventricular tachycardia.^{18,19} To date, studies examining ventricular deformation through cardiac MRI have primarily focused on correlating specific strain values with clinical parameters such as quality of life, symptoms, the presence of a ventricular septal defect patch, and remodelling after pulmonary valve replacement.^{14,18}

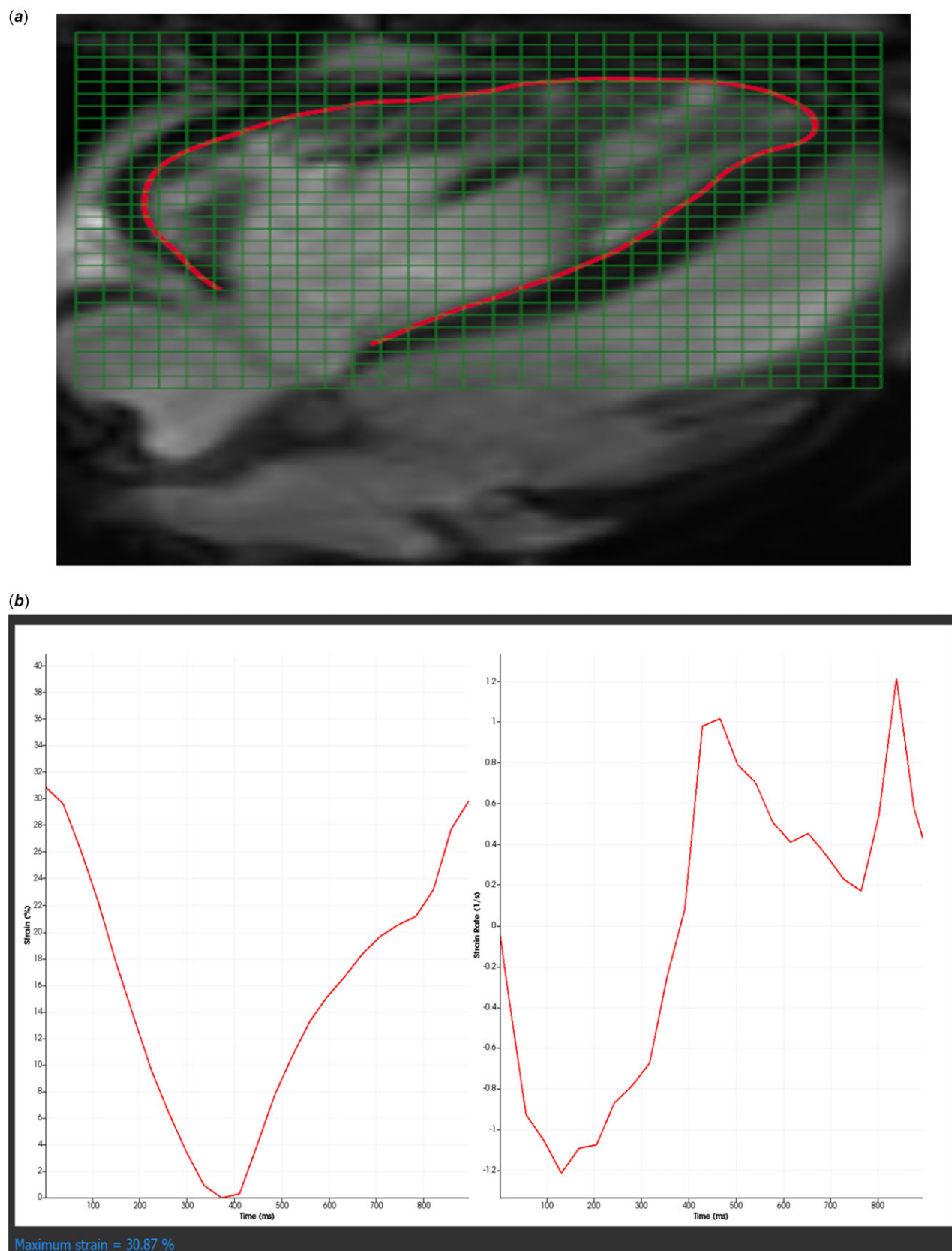


Figure 3. (a) Right Ventricular Global Longitudinal Strain measurement (b) Right ventricular global longitudinal strain rate analysis.

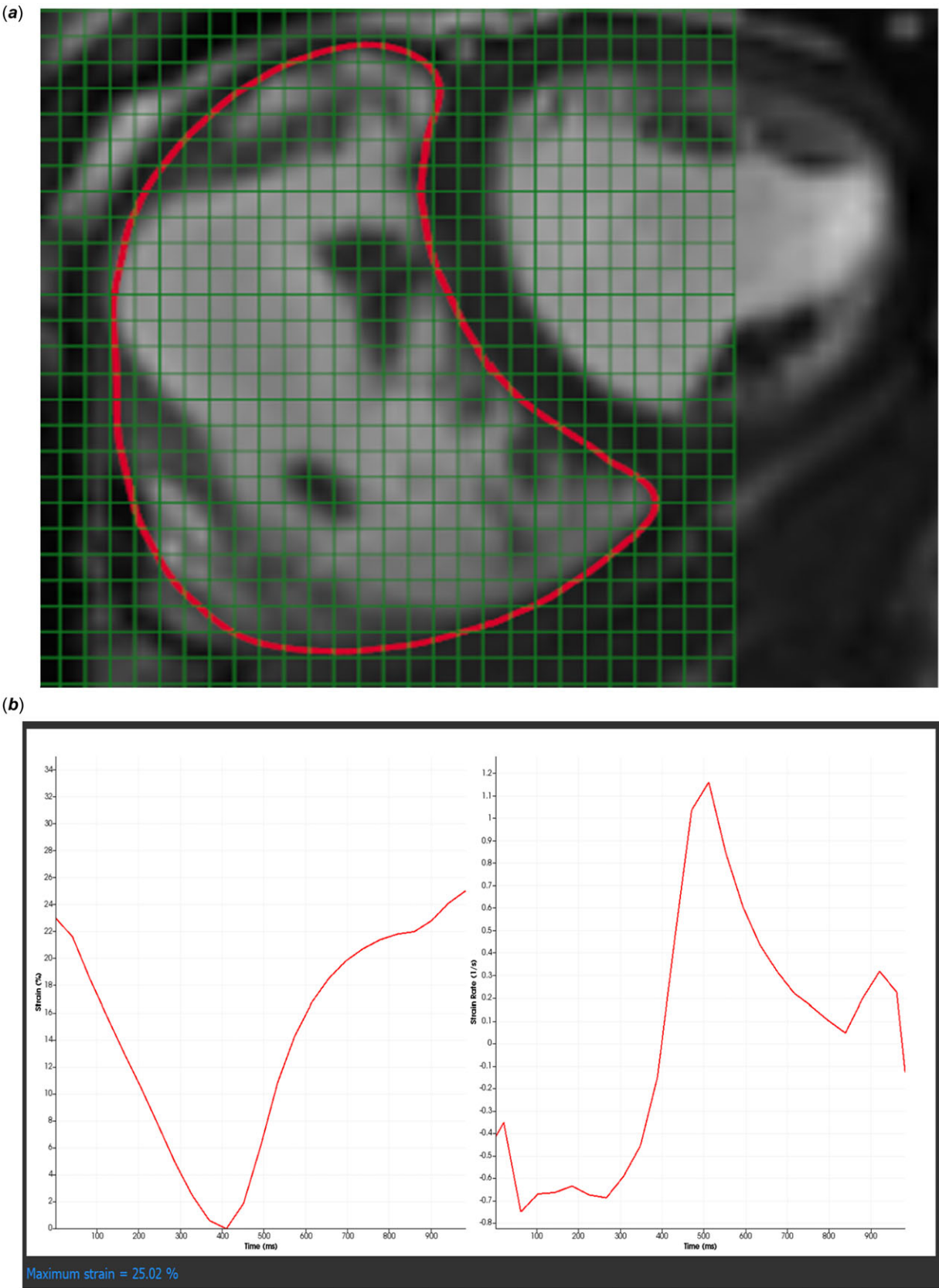


Figure 4. (a) Right ventricular global circumferential Strain measurement (b) Right ventricular global circumferential strain rate analysis.

Distinct adaptive responses in isolated pulmonary regurgitation and rTOF patients

It is noteworthy that our study revealed a consistent predominance of longitudinal strain in patients with pulmonary regurgitation, regardless of its underlying aetiology. The normal right ventricular myocardium consists of horizontally arranged superficial and deep myocardial fibres responsible for predominantly longitudinal contraction. This finding aligns with previous research indicating that the right ventricular response to the hemodynamic burden posed by regurgitant lesions tends to favour longitudinal strain as a compensatory mechanism.^{7,13–15,20,21} This response is well-documented and reflects the right ventricle's capacity to accommodate increased volumes by stretching in the longitudinal direction.^{15,16,20}

The relatively greater reliance on circumferential strain in rTOF was emphasised in our previous study and thought to be an adaptive mechanism related to the underlying myocardial architecture. Pathological studies have identified a more well-defined middle layer of circumferential fibres in hearts with TOF and pulmonary stenosis, which is not present in the normal right ventricle.²² The greater circumferential strain seen in rTOF compared to isolated pulmonary regurgitation is reflective of these findings and suggests that TOF patients may have a greater compensatory response based on the underlying myocardial architecture. Since this was noted to be present from birth, it is most likely a compensatory response during foetal development and not solely a result of increased right ventricular volumes. Whether this represents adaptive mechanisms designed to preserve right ventricular function or potentially maladaptive responses contributing to long-term sequelae remains unknown. It is important to recognise that this response may also be influenced by factors related to the surgical repair itself, such as a ventricular septal defect patch placement, right ventriculotomy, and the effects of cardiopulmonary bypass.²³ There is a lack of information on the underlying morphology on the right ventricular architecture in isolated pulmonary regurgitation due to valvar pulmonary stenosis which is clearly a different disease process to TOF. Based on our findings, we can only postulate that their circumferential fibres may be less well developed and perhaps more akin to the normal right ventricle. However, there was no significant difference between the two patient groups when comparing the age at time of intervention namely, TOF repair versus balloon pulmonary valvuloplasty ($P > 0.05$) as the vast majority of our patients underwent their repair or balloon valvuloplasty within the first year of age (Table 1).

Our current rTOF population had improved global longitudinal strain (-31.5%) compared to our previous study, where rTOF patients showed global longitudinal strain (-20%),¹⁰ likely due to the current rTOF population having relatively smaller right ventricular volumes. Interestingly, global circumferential strain in the current rTOF population (-26.5%) in comparison to our previous study (-17%), remained lower when compared to the control group (-32%).¹⁰ The consistently lower circumferential strain in rTOF at relatively smaller right ventricular volumes suggests that longitudinal strain is maintained while circumferential may be an earlier marker of functional decline. Furthermore, in the isolated pulmonary regurgitation group, the combination of a relatively preserved mean right ventricular ejection (54%) and a lower mean global circumferential strain (-22%) suggests an important adaptive mechanism. We believe this finding further underscores the reliance on global longitudinal

strain, with a mean value (-32%) in this group, to augment right ventricular ejection fraction as a compensatory response. This adaptation may, in turn, limit the utility of following right ventricular ejection fraction and global longitudinal strain in detecting early functional decline, as the right ventricle maintains its ejection fraction despite underlying deformation abnormality. Conversely, the reduction in circumferential strain reinforces its role as a potentially more sensitive marker of early functional deterioration, highlighting its potential clinical utility in identifying subtle ventricular dysfunction before overt declines in right ventricular ejection fraction become apparent.

In a secondary analysis comparing both the isolated pulmonary regurgitation and rTOF matched groups with larger right ventricles (Z -score >2), the isolated pulmonary regurgitation group continued to exhibit a lower mean global circumferential strain of -21% compared to -26% in the rTOF group ($p = 0.05$). Despite this difference, both groups maintained a similarly preserved right ventricular ejection fraction of 53 and 50% , respectively ($p > 0.05$), as well as comparable global longitudinal strain values of -31 and -32% , respectively ($p > 0.05$). These findings further support the notion that reductions in circumferential strain serve as an early indicator of subtle ventricular dysfunction, preceding overt declines in right ventricular ejection fraction typically identified through declines in longitudinal strain and ejection fraction. However, further studies are needed to validate this observation and better define its clinical implications.

Finally, and in another secondary analysis, we compared the 23% of isolated pulmonary regurgitation patients who underwent balloon pulmonary valvuloplasty outside of infancy to their matched counterparts in the rTOF group. Notably, no significant differences were found in global circumferential strain between the groups (-26% versus -26% , $p > 0.05$), and all other parameters were similarly comparable. This finding supports the hypothesis that prolonged exposure to pressure load, as seen in this isolated pulmonary regurgitation subgroup, may mimic some of the physiological changes observed in the rTOF group, leading to similar circumferential strain values. This suggests that the unique pathophysiology of rTOF, inclusive of pressure load, contributes to the development of a more robust circumferential myocardial layer in these patients.

Clinical implications and the role of guidelines

The findings of this study underscore the importance of assessing both circumferential and longitudinal strain patterns in patients with pulmonary regurgitation, particularly in different clinical contexts. The distinctions in strain responses observed between isolated pulmonary regurgitation and rTOF patients emphasise the need to measure both when approaching patient management. It remains unclear whether the clinical guidelines for determining the appropriate timing of pulmonary valve replacement, currently developed for repaired TOF patients, should be adapted for managing isolated pulmonary regurgitation following pulmonary stenosis relief. Further research is warranted to ascertain whether these strain patterns can serve as prognostic indicators, guiding the development of specific guidelines for isolated pulmonary regurgitation. While it may be appropriate to continue utilising the existing cardiac MRI guidelines based on right ventricular volumes and pulmonary regurgitant fraction for both patient groups, further research into alternative parameters and lesion-specific guidelines is required.

Limitations

Despite the valuable insights from our study, several limitations must be acknowledged. First, the retrospective nature of our analysis limits the ability to establish causality. Second, our study sample is relatively small that may affect the generalizability of our findings. Moreover, we did not include post-pulmonary valve replacement data, as post-pulmonary valve replacement cardiac MRI is not routinely performed in our practice. This restricts our ability to evaluate longitudinal changes and the impact of pulmonary valve replacement on right ventricular function and remodelling. Future prospective studies with larger cohorts and routine post-pulmonary valve replacement imaging are needed to validate our findings and provide a more comprehensive understanding of the long-term effects of pulmonary valve replacement on right ventricular deformation parameters.

In addition, the potential impact of a transannular patch, ventricular septal defect patch, and electrical conduction delays, such as right bundle branch block, on strain and strain rate must be considered, particularly given that these factors are present in the rTOF group but not in the isolated pulmonary regurgitation or control groups. Although efforts were made to mitigate this by sampling below the right ventricular outflow tract for global circumferential strain, variability in patch size may have influenced sampling location, leading to possible inconsistencies. In contrast, the isolated pulmonary regurgitation group had more uniform sampling. In addition, more apical sampling in some patients could have contributed to differences in global circumferential strain and is acknowledged as a limitation.

Conclusion

In conclusion, our findings emphasise that right ventricles in rTOF patients appear to rely on slightly enhanced circumferential deformation as a compensatory mechanism in response to increased volume loads more than isolated pulmonary regurgitation right ventricles due to their underlying myocardial architecture. This distinct adaptation suggests that rTOF right ventricles exhibit a heightened responsiveness to the volume burden compared to isolated pulmonary regurgitation right ventricles. These observations underscore the importance of considering the relative contributions of both circumferential and longitudinal strain patterns in the context of pulmonary regurgitation. Understanding these strain mechanisms is crucial for unravelling the intricate mechanisms underlying right ventricular dysfunction in pulmonary regurgitation. Further study to include post-pulmonary valve replacement deformation parameters is warranted to elucidate the impact of timing of pulmonary valve replacement in patients with pulmonary regurgitation, whether it is isolated or secondary to rTOF.

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Competing interests. The authors declare none.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Health Information Act of Alberta, Canada) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Health Research Ethics Board (HREB), University of Alberta, Edmonton, Canada).

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