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ORIGINAL PAPER

# Right atrial function early after tetralogy of Fallot repair

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## Abstract

Diastolic dysfunction after repair for Tetralogy of Fallot (TOF) is associated with adverse long-term outcomes. Right atrial (RA) mechanics as a proxy of right ventricular (RV) diastolic function in the early post-operative period after surgical repair for TOF has not been reported. We sought to evaluate RA and RV strain prior to hospital discharge after TOF repair and to identify important patient factors associated with strain using a machine learning method. Single center retrospective cohort study of TOF patients undergoing surgical repair, with analysis of RA and RV strain from pre-and post-operative echocardiograms. RA function was assessed by the peak RA strain, systolic RA strain rate, early diastolic RA strain rate and RA emptying fraction. RV systolic function was measured by global longitudinal strain. Pre- and post-operative values were compared using Wilcoxon rank sum test. Gradient boosted machine (GBM) models were used to identify the most important predictors of post-operative strain. In total, 153 patients were enrolled, median age at TOF repair 3.5 months (25th-75th percentile: 2.2- 5.2), mostly male (67%), and White (64.1%). From pre-to post-operative period, there was significant worsening in all RA parameters and in RV strain. GBM models identified patient, anatomic, and surgical factors that were strong predictors of post-operative RA and RV strain. These factors included pulmonary valve and branch pulmonary artery Z scores, birth weight, gestational age and age at surgery, pre-operative RV fractional area change and oxygen saturation, type of outflow tract repair, duration of cardiopulmonary bypass, and early post-operative partial arterial pressure of oxygen. There is significant worsening in RA and RV strain early after TOF repair, indicating early alteration in diastolic and systolic function after surgery. Several patient and operative factors influence post-operative RV function. Most of the factors described are not readily modifiable, however they may inform pre-operative risk-stratification. The clinical application of RA strain and the prognostic implication of these early changes merit further study.

**Keywords** Tetralogy of Fallot · Right atrium · Strain; Right atrial strain · Diastolic Dysfunction · Congenital Heart Disease

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## Abbreviations

| | |
|---|---|
| RA | Right atrium/ right atrial |
| RV | Right ventricle/ right ventricular |
| GBM | Gradient boosted quantile regression models |
| TOF | Tetralogy of Fallot |

## Introduction

Diastolic dysfunction after repair for Tetralogy of Fallot (TOF) is associated with adverse long-term outcomes, including worse RV systolic function, greater RV dilation, increased risk for re-interventions and ventricular tachycardia [1, 2]. Right atrial (RA) function has emerged as a measure reflective of RV diastolic function, and has been studied in the pediatric population [3, 4]. RA strain allows for quantitative assessment of RA deformation negating the effects of cardiac translational motion, with relative angle and tethering independence [5–7]. Use of RA deformation to assess RV diastolic function is possible because the atrium acts as a reservoir during maximal atrial filling (ventricular systole), a conduit (passive emptying during early ventricular diastole), and a booster pump, actively pumping in late diastole, completing ventricular filling [8–10]. Thus, the atrium acts as a modulator of ventricular filling and therefore the assessment of RA function can inform RV diastolic function. A "stiff" right ventricle, for example, results in an increase in RA reservoir function at first, without change in the passive conduit phase, but may increase the RA kick (pump) [10]. Studies showed that atrial deformation is impaired in adolescents and young adults with TOF [7, 11]. However, few studies have investigated RA deformation by echocardiography in infants with TOF early after surgical repair. Therefore, we sought to evaluate RA deformation utilizing strain measurements in the early post-operative period following TOF repair, and to identify predictors of post-operative RA and RV strain.

## Methods

### Study population and data collection

We conducted a retrospective cohort study of infants with TOF who were enrolled in a single-center study at the time of TOF surgical repair. The study included patients younger than 2 years of age undergoing surgical repair for TOF between May 1, 2012, and June 2, 2017, who had post-operative echocardiograms obtained prior to hospital discharge as part of a research protocol. Patients that had an aortopulmonary shunt or other palliative procedure (e.g., a stent in the RV outflow tract or in the ductus arteriosus) prior to TOF repair were included, and those who received a staged repair with unifocalization of the pulmonary arteries and conduit placement followed by later closure of the ventricular septal defect were excluded. The description of the cohort and study methods was previously published [12]. The study protocol was approved by the Institutional Review Board for the Protection of Human Subjects at Children's Hospital of Philadelphia, and parents of subjects gave informed consent to participating in the study.

### Echocardiography

Echocardiographic data collection included pre-operative (clinically indicated) and post-operative (research-based) echocardiograms. Post-operative echocardiograms were obtained between 2 and 5 days after TOF repair, according to the research protocol. Echocardiograms were performed on iE33 machines (Philips Medical Systems, Andover, MA). RA and RV strain were measured offline from pre-and post-operative echocardiograms using 2D speckle tracking TomTec software (Cardiac Performance Analysis software; TomTec Imaging, Unterschleissheim, Germany). RA reservoir function was assessed using peak RA strain, the main outcome in this study. Other RA strain derived measurements included systolic RA strain rate (reservoir function), early diastolic RA strain rate (conduit function), and RA emptying fraction (%), calculated as RA end-systolic volume minus RA end-diastolic volume, divided by the RA end-systolic volume. RA strain was measured on four-chamber cine-loop images that included the RA roof, and the atrial septum. (Figs. 1a–d) The RA tracing for strain was started and terminated 0.5 cm above the atrioventricular junction to avoid inclusion of RV myocardial movement. Manual adjustment of software automated tracing was performed as needed to approximate the atrial contour. RA emptying fraction was calculated as (maximal RA volume–minimal RA volume)/ maximal RA volume. We recorded the early diastolic strain rate but did not record the late diastolic strain rate because at this age it can be difficult to distinguish late from early strain rate. Images were measured in two cardiac cycles and the mean value was taken.

RV systolic function was assessed with RV global longitudinal strain from the apical four chamber view. RV global longitudinal strain was assessed by speckle-tracking analysis on four-chamber cine-loop images that included RV free wall and septum using TomTec software (Cardiac Performance Analysis, TomTec, Germany) by a single observer (YW) who was blinded to clinical characteristics, as in our prior study [13]. Images were obtained on iE33 echo machines (Philips Medical Systems, Andover, MA). Mean frame rates for analysis were $70 \pm 17$ Hz. Absolute values of strain are used to describe increase or decrease in RV strain. Since the interval between the pre- and post-operative echocardiograms was short, we chose not to index strain-derived atrial volumes to body size.

For assessment of post-operative pulmonary insufficiency, we used the pulmonary artery diastolic to systolic time-velocity integral ratio (DSTVI), obtained from interrogation of the proximal to mid main pulmonary artery with continuous wave (CW) Doppler. Based on our prior studies, a DSTVI ratio of 0.49 (95% CI: 0.44–0.56) and 0.72 (95% CI: 0.68–0.76) correspond to regurgitant fractions of 20–40% and $\geq 40\%$ by cardiac magnetic resonance imaging, respectively. [14, 15].

RA strain measurements were performed by a single observer blinded to clinical characteristics (OE). RV strain was measured by a single observer (YW) blinded to clinical information, with a prior excellent intra-observer reliability. [16].

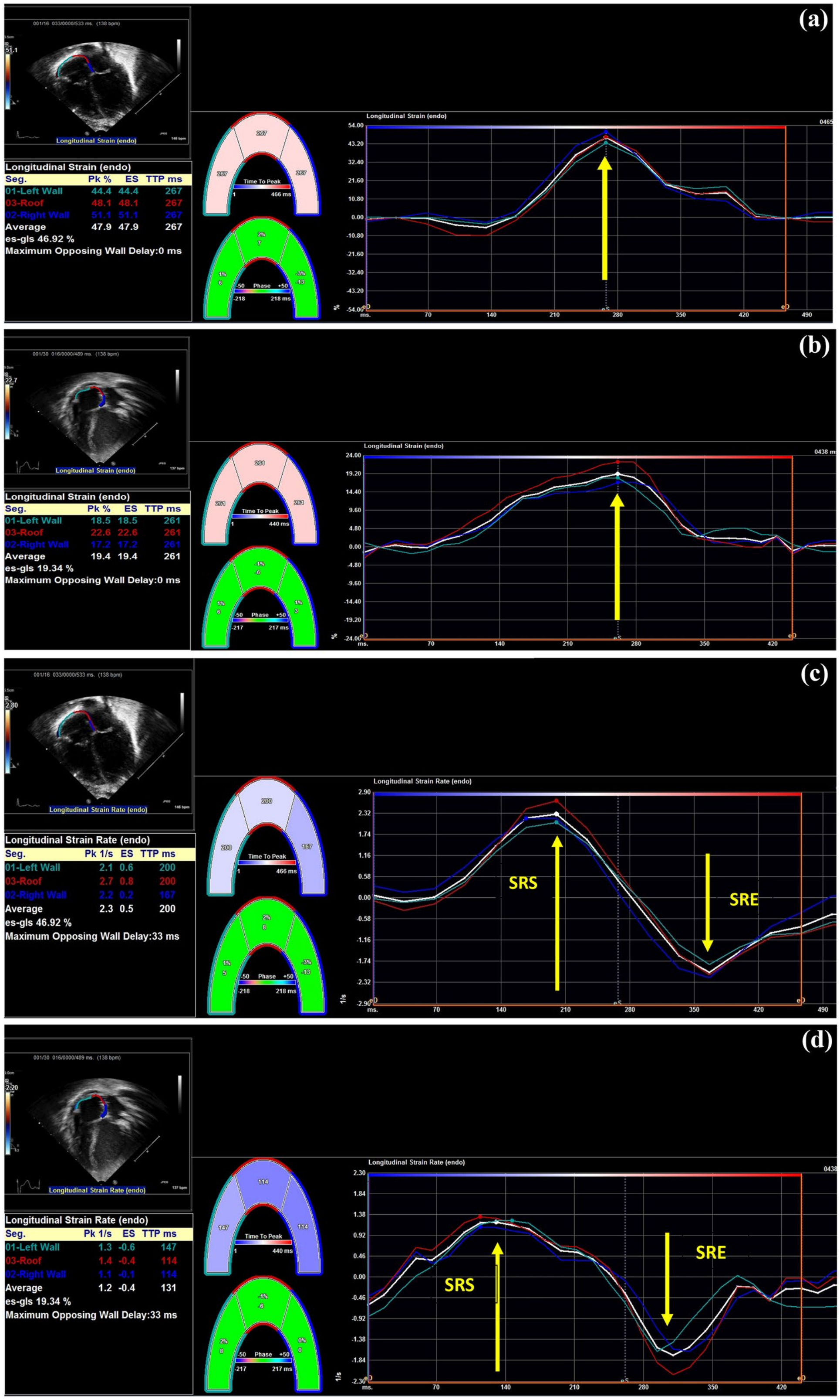


**Fig. 1** Examples of pre-operative and post-operative right atrial strain measurements. **a** Measurement of pre-operative RA peak strain: the arrow indicates the average value for the pre-operative PA peak strain. **b** Measurement of post-operative RA peak strain: the arrow indicates the average value for the post-operative PA peak strain. **c** Measurement of pre-operative systolic RA strain rate: arrows indicate the peak systolic (positive) strain rate (SRS) and the early negative (diastolic) strain rate (SRE). **d** Measurement of post-operative systolic RA strain rate: the arrows indicate the peak systolic (positive) strain rate (SRS) and early negative (diastolic) strain rate (SRE)

## Clinical data

Several patient and operative characteristics were recorded. Demographic characteristics, gestational age, birth weight, presence of genetic syndrome, presence of extracardiac malformations, and age at TOF repair were recorded. TOF anatomy included pulmonary stenosis, pulmonary atresia, TOF with absent pulmonary valve, and TOF with complete atrioventricular canal defect. Type of TOF surgical repair included closure of the ventricular septal defect with or without need for relief of RV outflow tract obstruction. RV outflow tract interventions included: transannular patch, non-transannular patch, pulmonary valvotomy, and placement of a right ventricle to pulmonary artery conduit. Intracardiac access included transatrial with or without ventriculotomy. Intra-operative and immediate post-operative characteristics were included, including number and duration of cardiopulmonary bypass runs, total aortic cross-clamp time, and early post-operative arterial oxygen content (first 24 h after TOF repair). Because the outcomes of interest were post-operative RA and RV function, we only included factors that occurred prior to TOF repair, such as demographic and anatomic characteristics, surgical factors, and early post-operative arterial partial pressure of oxygen [12] in the Gradient Boosted Machine analysis. The outcomes of interest were post-operative peak RA strain, systolic RA strain rate, early diastolic RA strain rate, and RV global longitudinal strain.

## Missing data

We included the same patient characteristics (including demographics and pre-surgical clinical factors) and operative characteristics in all statistical models for the 4 outcomes, all of which were measured before the post-operative strain outcome measures. Because most data for this analysis was derived from a prospective study, we had excellent data acquisition with minimal missing data. Missing data were imputed using a fully conditional specification (FCS) method for categorical and continuous characteristics using 10 imputations with the SAS Procedure Proc MI. Each GBM was run on each imputed dataset and the results across the 10 imputed datasets were averaged.

## Statistical analysis

### Descriptive statistics and reliability

The cohort is described using frequencies and percentages for categorical characteristics or median (25th-75th percentile) for continuous measures. Pre-operative and post-operative measurements of peak RA strain, systolic RA strain rate, early diastolic RA strain rate, and RV global longitudinal strain were compared using Wilcoxon Rank Sum tests. We first identified changes in strain parameters from pre- to post-operative. Next, we evaluated predictors of post-operative strain (main outcome).

Intra- and inter-observer reproducibility for RA strain were assessed in 10 and 12 randomly selected echocardiograms, respectively. Inter-observer reproducibility was evaluated between readers OE and YW. Intra-class correlation coefficients (ICCs) were calculated a priori and are presented as ICC (95% confidence interval). ICC was considered moderate if 0.50–0.74, good if 0.75–0.90, and excellent if > 0.90.

### Gradient boosted machines (GBM)

The statistical analysis used gradient boosted quantile regression trees to measure the relative importance of each patient characteristic for each strain outcome. For each imputed dataset, 70% of the data were used as training data for model development and 30% as the holdout testing set for model evaluation. On each imputed training dataset, a threefold cross-validated (CV) gradient boosted machine (GBM) was performed using 5000 gradient boosted trees and determined the optimal number of trees which minimized the cross validated root mean square error (RMSE). Each GBM provided a relative importance score for all of the variables included in the model and the relative importance scores across 10 multiply- imputed datasets were averaged. Average RMSE were calculated across the 10 imputed datasets for the training data and testing data. Lower RMSE indicates better prediction accuracy. Models were run with and without the pre-operative strain values. GBMs were run using the GBM package in R 3.4.3 (R Development Core Team, Vienna, Austria) [17]. We set alpha = 0.05 for all analyses with two-tailed p-values. All analyses were performed using SAS Software version 9.4 (SAS Institute, Cary NC) and Stata 14.2 (College Station, TX) for ICC calculations.

## Results

In total, 153 of the 158 patients enrolled in the original cohort study were included in this analysis. Five patients were excluded due to suboptimal image quality for RA strain analysis. Most patients were male (62%), non-Hispanic white (64.1%), and non-Hispanic black (9.8%). 22q11.2 deletion syndrome was present in 7.9% of patients. Most patients had TOF with pulmonary valve stenosis (81.7%). The median age at repair was 3.5 months (25th-75th percentile: 2.2–5.2). Median length of hospital stay was 8 days (25th-75th percentile: 6–13). Post-operative echocardiograms were performed 3 days after surgery (25th-75th percentile: 2–5 days), as dictated by the study protocol. All patients had a transatrial approach. Of those, 65% also had a transventricular approach. We compared surgical access (transatrial, transatrial and ventricular, transventricular) and there was no statistically significant change in RA peak systolic strain, RA systolic strain rate, RAEF or RA early strain rate. Post-operatively, there was evidence of greater than mild pulmonary insufficiency with a median DSTVI ratio of 0.56 (25th-75th percentile: 0.39, 0.75). Of the 137 patients with evaluable MPA Doppler tracings, 61 patients (44.5%) had antegrade end-diastolic flow in the main pulmonary artery. There were 125 patients with a patent foramen ovale after TOF repair (75.1%), of whom 55 had right to left flow, 50 had bidirectional flow, and 10 had left to right flow. Other characteristics are detailed in Table 1.

Good inter-observer reproducibility was demonstrated for strain measurements (Table 2).

There was significant decrease in peak RA strain, systolic RA strain rate, early diastolic RA strain rate, RA emptying fraction, and RV global longitudinal strain between pre- and post-operative echocardiograms. (Table 3) Peak RA strain decreased in most patients (n = 133; 93%) and RA end-diastolic and end-systolic volumes increased from the pre- to the post-operative period.

There were no significant associations between change in RA function parameters from pre- to post-operative with DSTVI, however post-operative peak RA strain and RAEF were modestly associated with post-operative DSTVI severity of pulmonary insufficiency (rho = 0.24, p = 0.012 and rho = 0.19, p = 0.048, respectively).

We found a direct association between post-operative RV free wall strain rate and RA systolic strain rate, and post-operative RV free wall strain seemed to predict RA peak systolic strain and RA early SR as seen in Table 4.

There were 39 patients (25%) with a follow up catherization or reoperation. 35 had a cardiac catheterization and 21 patients that had a reoperation. Some patients had several catheterization and two patients had more than one reoperation. We examined whether post-operative RA strain or changes in strain were associated with the odds of a follow up catheterization or reoperation (called an event). We found that higher post-operative RA strain was associated with greater odds of an event (OR 1.04, 95% CI 1.002, 1.074, p = 0.04). Post-operative RA strain was 23.9 (IQR 17.6, 30.1) in those that had a subsequent event, as compared to 19.50 (IQR 13.8, 29.8) in those without a subsequent event. However, the 2-group comparison using the Mann Whitney U test revealed a p value of 0.0849). No other RA parameters or changes in RA parameters were associated with odds of a post-operative event.

GBM models identified several patient and operative factors as predictors of the four post-operative strain outcomes. Conclusions reached from the GBMs with and without the pre-operative strain measurements were similar (data not shown). Pre-operative patient factors included birth weight, gestational age, pulmonary valve and branch pulmonary

**Table 1** Demographics, pre- and post-operative echocardiographic characteristics

| | |
|---|---|
| Non-Hispanic white, n (%) | 94 (64.1) |
| 22q11.2 deletion syndrome, n (%) | 12 (7.8) |
| Age at TOF repair, months | 3.5 (2.20- 5.20) |
| TOF repair with transannular patch, n (%) | 90 (58.8) |
| Length of hospital stay after TOF repair (days) | 8 (6, 13) |
| Pre-operative echocardiographic variables | |
| Pulmonary valve stenosis, n (%) | 125 (81.7) |
| Pulmonary valve Z -score | – 2.04 (– 2.59, – 1.43) |
| Right pulmonary artery Z-score | – 1.13 (– 1.79, – 0.47) |
| Left pulmonary artery Z-score | – 1.29 (– 1.96, – 0.38) |
| RV Fractional Area Change, (%) | 46 (42, 50) |
| Post-operative echocardiographic variables | |
| RV Fractional Area of Change, (%) | 41 (34, 45) |
| MPA DSTVI ratio* | 0.56 (0.39, 0.75) |
| MPA end-diastolic flow present, n (%) ** | 61 (44.5) |
| Patent foramen ovale *** | |
| Right to left flow | 55 (36.0) |
| Left to right flow | 10 (6.5) |
| Bidirectional flow | 50 (32.7) |

Categorical variables are presented as frequencies (%); continuous variables are presented as median (25th-75th percentile)

*Main pulmonary artery diastolic to systolic time-velocity integral ratio, higher ratio indicates greater pulmonary insufficiency

**Main pulmonary artery end-diastolic flow was not available in 16 patients

***A patent foramen ovale was present in 115/153 patients (75.2%)

**Table 2** Inter-observer reproducibility of RA function parameters

| Right atrial parameters | Preoperative ICC | Post-operative ICC |
|---|---|---|
| Peak RA strain | 0.62 (95% CI: 0.33; 1.02) | 0.96 (95% CI: 0.91; 1.01) |
| RA systolic strain rate | 0.83 (95% CI: 0.62, 1.02) | 0.86 (95% CI: 0.69, 1.03) |
| Early diastolic RA strain rate | 0.86 (95% CI: 0.69, 1.03) | 0.60 (95% CI: 0.23, 0.97) |
| RA end-systolic volume | 0.92 (95% CI: 0.82, 1.02) | 0.95 (95% CI: 0.89, 1.00) |
| RA end-diastolic volume | 0.81 (95% CI: 0.59, 1.03) | 0.93 (95% CI: 0.86, 1.01) |
| RA emptying fraction | 0.74 (0.45; 1.02) | 0.85 (0.70; 1.01) |

**Table 3** Right atrial and right ventricular strain measurements

| Measurement | Pre-operative* | Post- operative* | Difference** | P value |
|---|---|---|---|---|
| RA peak strain | 43.20 (34.40, 53.10) | 20.20 (16.20,29.40) | -22.10 (17.5) | < 0.0001 |
| RA early diastolic strain rate | − 1.90 (− 2.30, − 1.52) | − 1.20 (− 1.60, − 0.90) | 0.59 (1.02) | < 0.0001 |
| RA systolic strain rate | 1.80 (1.40, 2.10) | 1.40 (1.00, 2.00) | -0.27 (0.94) | 0.0003 |
| RA end-diastolic volume | 1.66 (1.09, 2.69) | 3.29 (2.06, 4.67) | 1.42 (1.88) | < 0.0001 |
| RA end-systolic volume | 3.75 (2.39, 5.77) | 5.23 (3.51, 6.86) | 0.86 (2.96) | 0.0002 |
| RA emptying fraction (%) | 56.18 (46.30, 63.07) | 36.14 (25.63, 43.53) | -18.60 (16.03) | < 0.0001 |
| RV global longitudinal strain | − 19.00 (− 21.60, − 15.30) | − 13.80 (− 17.05, − 10.00) | 4.60 (5.54) | < 0.0001 |
| RV end-diastolic volume | 1.69 (1.15, 2.69) | 3.29 (2.06, 4.67) | 1.29 (0.31; 2.33) | < 0.0001 |
| RV end-systolic volume | 3.77 (2.52, 5.77) | 5.23 (3.50, 6.86) | 0.70 (-1.1, 2.47) | 0.0033 |

Strain rate and RV global longitudinal strain are negative values (more negative values indicate better function), whereas RA peak strain and peak systolic strain rate are positive values

*Presented as median (25th-75th percentile)

**Difference: post-operative minus pre-operative mean values. RA volumes increased from pre-to post-operative measurements. Strain parameters and RA emptying fraction worsened

**Table 4** Correlations between post-operative RA and RV strain

| Parameter | Spearman rho | p-value |
|---|---|---|
| RA systolic SR and RV FWSR | − 0.32 | 0.0004 |
| RA early SR and RV FWSR | 0.50 | < 0.0001 |
| RA peak systolic strain and RVFW | − 0.23 | 0.047 |

*FW* free wall strain, *FWSR* free wall strain rate, *SR* Strain rate

artery Z scores, age at surgery, RV fractional area change and oxygen saturation. Operative factors included the type of outflow tract repair (for example, transannular patch, pulmonary valvotomy) duration of cardiopulmonary bypass, and early post-operative partial arterial pressure of oxygen. The 20 highest ranked factors and factors that had a relative importance > 1 are depicted in Figs. 2, 3. 4, 5. The average

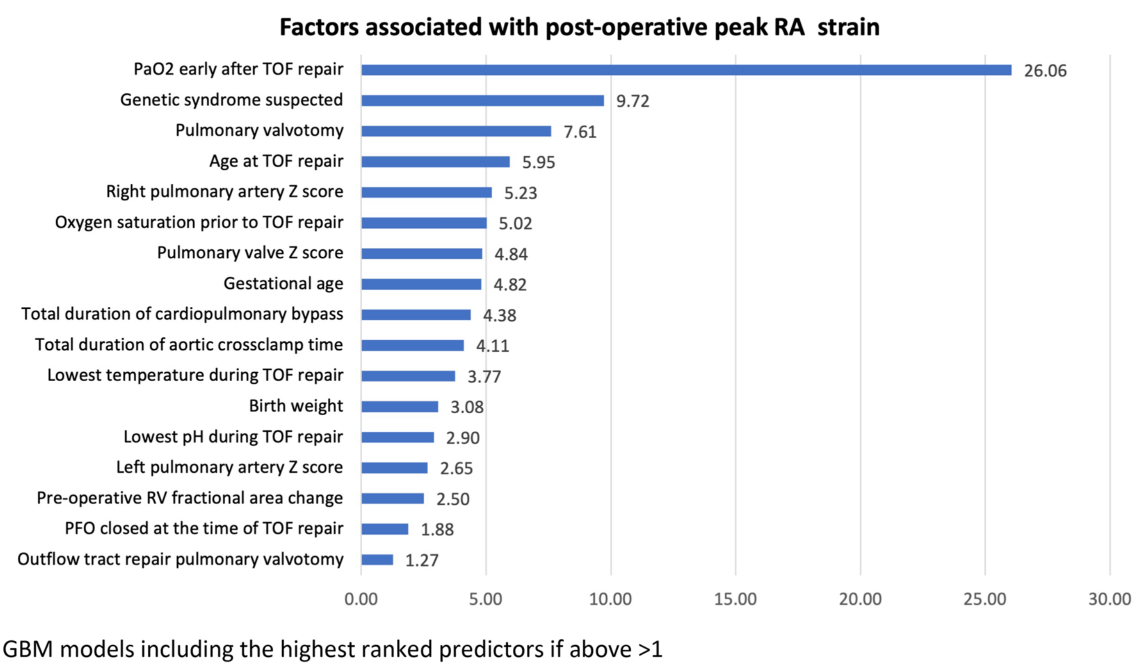


**Fig. 2** Predictors of RA peak strain identified by GBM

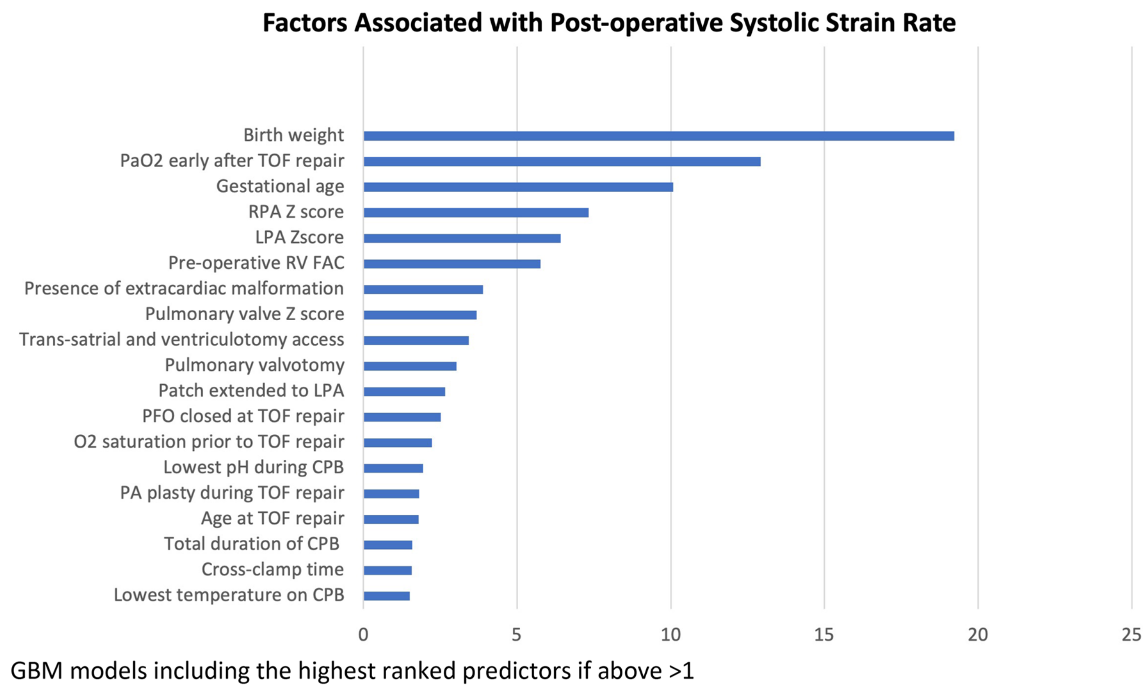


**Fig. 3** Predictors of systolic RA strain rate identified by GBM

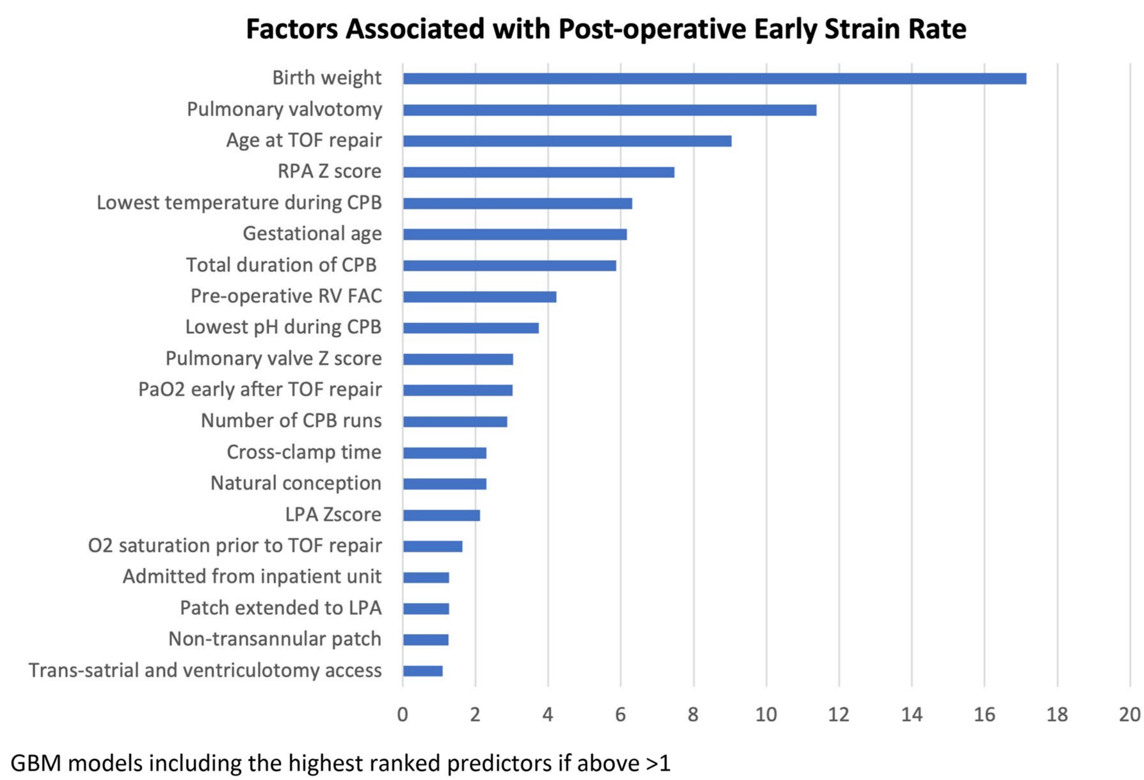


**Fig. 4** Predictors of RA early strain rate identified by GBM

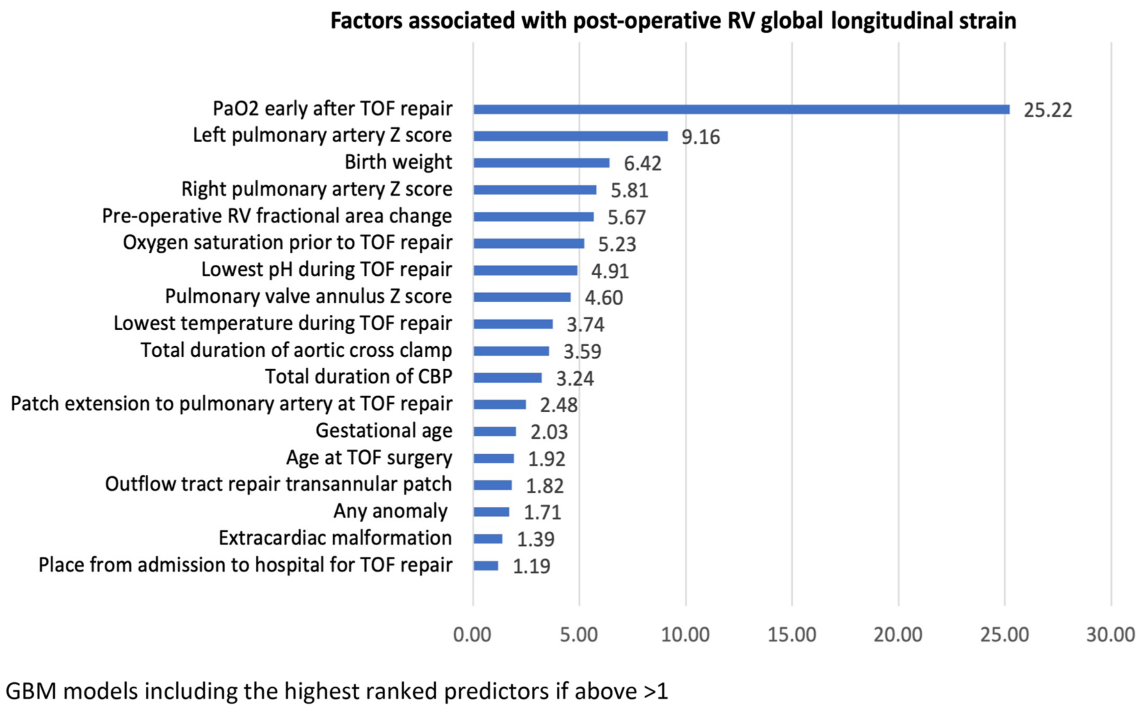


**Fig. 5** Predictors of RV global longitudinal strain identified by GBM

**Table 5** Average RMSE for training and test data across 10 imputed datasets

| Outcome | Training | Test |
|---|---|---|
| Peak RA strain | 2.05 | 10.80 |
| Systolic RA strain rate | 0.57 | 0.56 |
| Early diastolic RA strain rate | 0.52 | 0.59 |
| Global longitudinal strain | 1.42 | 4.26 |

Interpretation: Lower RMSE values indicate better prediction accuracy. There was greater prediction accuracy for post-operative systolic strain rate and post-operative early diastolic strain rate

RMSE values are presented for test and training data for each outcome, which shows, on average, greater prediction accuracy for post-operative systolic strain rate and post-operative early diastolic strain rate (Table 5).

## Discussion

In this study, we had two objectives: (1) to evaluate pre- to post-operative changes in RA and RV function in patients with TOF prior to and after surgical repair; and (2) to identify predictors of early post-operative RA and RV strain, which are proxy measures of RV diastolic function and RV systolic function, respectively. The study demonstrated significant worsening in all strain parameters from the pre-operative period to post-operative days 2 and 5 following TOF repair and identified several patient and operative predictors of post-operative strain.

The assessment of atrial function has emerged as a useful tool in the evaluation of ventricular diastolic function [9, 18]. Prior studies investigated the importance of RA function to inform RV diastolic dysfunction and outcomes in older patients with TOF and in those with pulmonary hypertension [3, 19–24]. The present report includes neonates and infants that were studied at the time of TOF surgical repair, to our knowledge the first report of RA strain in young patients with TOF. We found that all RA strain parameters and RV global longitudinal strain worsened significantly in the early post-operative period after TOF repair. Since the post-operative echocardiograms were performed between post-operative days 2–5 per research protocol, the changes in diastolic and systolic function are likely reflective of the early RV adaptation to TOF surgery. Diastolic dysfunction early after TOF repair has been described using the antegrade end-diastolic pulmonary artery flow as a corollary to diastolic dysfunction, also referred to as restrictive RV physiology, which was present in our study in almost half of the patients with evaluable MPA Doppler tracings [25–27]. When present early after TOF repair, this phenomenon was associated with low-cardiac output and slow post-operative recovery [28, 29]. Although restrictive physiology has been well-investigated, few studies have examined echocardiographic parameters with which to assess RV diastolic function early after TOF repair. Ye et al. demonstrated significant changes in tricuspid Doppler inflow velocities as well as systolic and diastolic RV strain rate 6–12 months after TOF repair in a group of patients undergoing TOF repair at around 3 years of age [30]. While not directly comparable to our results, this study demonstrated that the plasma biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) measured in the pre-operative period may be an adequate estimator of post-operative systolic strain parameters [30]. Studies in patients years after TOF repair reported reduced RA function with impaired pump, conduit, and reservoir function. These studies do not compare with our findings because we measured strain in the early post-operative period, but we do wonder whether RA function remains abnormal after TOF repair [7, 19, 31]. Given that the assessment of diastolic function using tricuspid inflow and myocardial velocities has limitations in young children with TOF [32], we offer RA strain as a possible means of assessing RV diastolic function in the post-operative period, although we recognize that this measure needs further study, in particular validation against biomarkers and clinical parameters.

Our study also demonstrated significant associations between post-operative RV free wall strain and RA systolic strain rate, RA early strain, and post-operative RA peak strain. These associations suggest an interplay between the atrium and the ventricle. Further, there is a possible compensatory mechanism of the right atrium the context of RV dysfunction. This finding was previously reported in patients after TOF repair by Hui et al. [18] Also similarly to our findings, Abd El Rahman et al. demonstrated similar correlations between RA peak longitudinal strain and RV strain, connoting a robust right atrio-ventricular coupling. [33].

While we didn't demonstrate associations between change in pre- to post-operative RA function parameters with post-operative pulmonary insufficiency (as a surrogate of volumetric changes in the post-operative period), we did find a direct association between post-operative RA peak strain and RAEF with DSTVI. These associations suggest appropriate right atrial response to volume loading and speak to the impact of TOF surgery on right atrial changes. A similar finding was reported in patients with of relatively higher right atrial peak diastolic strain in patients with lower RV EF indicative of RV dysfunction, suggesting a similar compensatory possibility in which right atrial pump function is enhanced. [18].

We also showed increases in RA end- diastolic and systolic volumes with a greater magnitude of change in diastolic volume, resulting in a decrease in RV emptying fraction from the pre- to the post-operative period. Decreased right atrial function in the post-operative period after TOF repair is likely multifactorial, including the effect of pericardiotomy, the right atrial incision at the time of TOF repair in most patients, and acute changes in loading conditions after TOF repair, contributing to post-operative right-sided dysfunction. Riesenkampff et al.compared RA function in youth with repaired TOF to those with residual pulmonary insufficiency after balloon angioplasty for isolated pulmonary stenosis. They showed significant RA dysfunction in the repaired TOF group, suggesting impairment in right atrial function may be related to factors other than volume changes from pulmonary insufficiency. Operative factors such as right atrial scar and loss of pericardial integrity may also contribute to RA dysfunction in these patients [34]. These changes can also result from maintenance of adequate intravascular status after cardiopulmonary bypass and partly from early establishment of pulmonary insufficiency, given that most patients had TOF repair with a transannular patch and the DSTVI ratio indicates early pulmonary insufficiency. In our prior report from this cohort in a small subset of patients undergoing cardiac magnetic resonance imaging prior to hospital discharge from the TOF repair admission, we showed significant pulmonary insufficiency, with a mean regurgitant fraction of $27 \pm 16\%$, with persistently elevated RV mass but no development of RV dilation. That study did not assess changes in right atrial volumes. [35].

Finally, we report several patient pre- operative and operative factors that are associated with all post-operative strain parameters measured in this study. Notably, the arterial content of oxygen upon arrival to the intensive care unit after TOF repair was a highly ranked predictor of post-operative RA and RV strain. Arterial desaturation after TOF repair is a clinical marker of elevated right filling pressures and post-operative diastolic dysfunction, when the foramen ovale serves as a "pop-off" valve allowing for right to left flow resulting in systemic desaturation [36]. This finding, along with the prevalence of right to left shunting at the atrial level in our study, lends validity to our models. Other predictors identified in this study are known risk factors for post-operative systemic desaturation, post-operative diastolic and systolic dysfunction, and a protracted post-operative course, as shown in prior studies, including our own report [12, 26–28, 36, 37]. We used a novel methodological approach with machine learning methods, which have not been used to investigate post-operative function after TOF repair. Machine learning was used in a study of infants with single-ventricle physiology, using naïve Bayesian network models to predict critical events that occurred 1 to 8 h prior to a post-operative complication [38]. The objective of our study was to apply machine learning methods to identify a set of factors associated with post-operative strain, rather than use a more conventional approach like linear regression, which would yield fewer associations and would not provide a ranking of predictors. As such, several factors identified are markers of TOF disease severity. For example, gestational age, birth weight and age at TOF repair are relevant patient risk factors that, although not readily modifiable, can inform risk stratification prior to TOF surgery.

Anatomical factors, including the size of the pulmonary valve and pulmonary arteries also imply disease severity and thus can be associated with worse function after surgery. Intra-operative factors might be considered surrogates of a complex surgical procedure, including duration of cardiopulmonary bypass and cross clamp, type of intra-cardiac access (such as trans-atrial or ventriculotomy), and type of outflow tract repair. We also report that extracardiac malformations are associated with post-operative strain. A study by Knuf et al.proposed pre-operative risk-stratification of patients with TOF based on severity of cyanosis/pulmonary valve anatomy and other malformations, cardiac and non-cardiac. They found that cardiac and extra-cardiac malformations and intra-operative factors conferred significant perioperative risk to patients undergoing TOF repair at a median age of 12 months (but including neonatal TOF repairs as well [39]. This study shares similarity with our report in that patient and intra-operative factors are important determinants of post-operative course, and in our case, post-operative function measured as strain. In summary, we present a novel analytical approach to investigate factors associated with post-operative RA and RV strain. These could be considered in risk stratification prior to TOF repair. While use of RA strain in the post-operative period warrants more study and development as an echocardiographic measurement for bedside use, we propose that RA function may further the assessment of RV diastolic function, which remains limited at present.

We acknowledge limitations to our study. The reliability of atrial strain in young populations is not yet well-established. It is our intention that this study add to the compendium of knowledge that standardizes this tool. Two-dimensional speckle tracking of the RA has inherent tracking difficulties due to the thinner atrial wall compared with that of the ventricle. However, obtaining protocolized post-operative echocardiograms within 2–5 days from surgery is a strength of this study, which reflects early post-operative RA and RV function independently of clinical status, and thus limits selection and referral bias. Post-operative reproducibility of RA strain was superior to the pre-operative reproducibility, possibly because post-operative echocardiograms were obtained as part of a research protocol, resulting in superior image quality for reproducible tracings of the right atrium. Lack of protocolized pre-operative echocardiograms is a limitation of this study. However, RA strain measurements were retrospectively measured both in the pre- and post-operative echocardiograms (post-operative echocardiograms were obtained as part of the research study). A possible limitation is the inclusion of patients with various pulmonary valve anatomies, but this confers greater generalizability to patients with TOF that undergo surgical repair in the first few months of life. Further, having performed echocardiograms within a strict time window might have hampered our ability to identify patients with greater degrees of ventricular dysfunction should dysfunction be more apparent beyond the immediate post-operative period. In addition, our analyses did not account for use of vasopressors, which may lead to changes in strain. Since this study sought to compare changes in strain and associations between pre- and intra-operative factors associated with post-operative strain, we did not account for use of vasopressors, which could have been concurrent with strain measurements. It is important to note, however, that a minority of patients in this study received inotropic support beyond post-operative day 3. We do not report follow-up data on RA strain, since our objective was to evaluate early changes in RA strain after TOF repair. Finally, the research-based nature of post-operative echocardiograms allowed for minimal missing data, reducing bias and increasing the power of the study.

In conclusion, this initial report offers an assessment of RA and RV function early after TOF repair. Changes in RA strain could reflect early post-operative RV diastolic dysfunction which is influenced by several patient and operative factors. RA strain needs to be studied longitudinally to determine whether RA function recovers after the early post-operative period and whether this measure is associated with long-term RV function.

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## Declarations

**Conflict of interests** The authors have no relevant financial or non-financial interests to disclose.

**Ethical approval** The study protocol was approved by the Institutional Review Board for the Protection of Human Subjects at Children's Hospital of Philadelphia, and parents of subjects gave informed consent to participating in the study.

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