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Longitudinal Changes in Right Ventricular Function in Tetralogy of Fallot in the Initial Years after Surgical Repair

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Abstract

Background—Right ventricular (RV) dysfunction is associated with adverse long-term outcomes in tetralogy of Fallot (TOF). Little is known about RV function in the first years after surgical repair. We sought to investigate perioperative changes in myocardial deformation using global longitudinal strain.

Methods—We performed a retrospective analysis of surgically repaired TOF patients. Global longitudinal peak systolic RV strain was measured on early post-operative, two subsequent post-operative echocardiograms through two years post-operatively, and pre-operative echocardiograms, when available. Pre-operative and late follow-up strain was compared to 0–8 month and 1–4 year-old controls, respectively.

Results—Forty-seven patients were included. Compared to post-operative strain (7 ± 7 days post-operatively), strain at follow-up 1 (8.3 ± 4 months post-operatively) was significantly improved ($-12.3 \pm 3.3\%$ vs. $-18.8 \pm 2.5\%$ $p < 0.001$), with no additional improvement to follow-up 2 (23.2 ± 6 months post-operatively, $-18.8 \pm 2.5\%$ vs. $-19.8 \pm 3.1\%$, $p = 0.12$). Post-operative strain was worse than pre-operative strain ($n = 25$, $-12.5 \pm 3.6\%$ vs. $-18.4 \pm 2.9\%$, $p < 0.001$).

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CONFLICTS OF INTEREST

None

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Compared to controls, pre-operative strain was similar ($-19.3 \pm 3.8\%$ vs. $-18.4 \pm 2.9\%$, $p=0.3$), though late follow-up strain was significantly worse ($-27.7 \pm 2.8\%$ vs. $-19.8 \pm 3.1\%$, $p<0.001$).

Conclusions—RV global longitudinal strain worsens in the early post-operative period following surgical repair for TOF but recovers through two post-operative years. Despite recovery to pre-operative values, the presence of RV dysfunction compared to controls suggests that long-term dysfunction may begin early. The trajectory of RV dysfunction through the later years needs further study.

Keywords

Tetralogy of Fallot; Right Ventricle; Strain; Perioperative; Congenital heart disease

BACKGROUND

Patients operated for tetralogy of Fallot (TOF) are at risk for right ventricular (RV) dysfunction, an important predictor of long-term adverse outcomes such as ventricular arrhythmias and sudden death.^{1–4} In the early post-operative period following initial TOF repair, RV dysfunction is associated with longer need for intensive care as well as longer need for inotropic support.⁵ However, there is little information about RV function in the window between surgery and the onset of long-term complications. It remains unclear whether RV dysfunction, when present, is established perioperatively, or whether it develops gradually in association with the long-term effect of residual lesions, such as pulmonary regurgitation. Better understanding of RV function in the initial years after surgery may better inform long-term outcomes.

Strain measured by echocardiography is a valid method to quantify function using regional myocardial deformation, with good correlation with ejection fraction by cardiac magnetic resonance.^{6–8} RV strain detects subclinical changes in function and predicts adverse outcomes in adults with heart failure.⁹ Despite its potential benefits, strain has not been used to assess early changes in function in an infant patient population undergoing surgical repair for TOF.^{4,10–12} The goals of this study were to examine early longitudinal changes in RV function and the risk factors associated with RV dysfunction as measured by strain in infants operated for TOF. We hypothesized that strain would worsen post-operatively but improve through two years following repair, and the postoperative worsening would be associated with neonatal repair and younger age at time of repair.

METHODS

Study population and Data Collection

This study was approved by the Institutional Review Board for the Protection of Human Subjects at The Children's Hospital of Philadelphia. We performed a retrospective cohort study of patients with TOF undergoing complete surgical repair between January 2011 and December 2012. Complete repair was defined as ventricular septal defect (VSD) closure with relief of right ventricular outflow tract (RVOT) obstruction. Inclusion criteria consisted of patients who had complete TOF repair and had follow-up at our institution, and those with adequate images for strain measurements on pre-discharge post-operative

echocardiograms. Patients followed at other institutions, those who required isolated VSD closure, had TOF in association with complete common atrioventricular canal, or those who died within the first two years following repair were excluded from our study.

Echocardiograms

Images were reviewed offline for suitability for use in the study on echocardiograms performed post-operatively prior to hospital discharge, and on two follow-up studies (echocardiograms through the first and second post-operative years, respectively) following repair. If available, pre-operative images were reviewed and analyzed for subgroup analysis. Images were considered suitable if the entire RV free wall was within the frame for at least one beat on four-chamber images. When multiple echocardiograms were present, those closest to surgery (post-operative) and closest to six months (follow-up 1) and two years (follow-up 2) following repair were utilized for review. Strain measurements were attempted on pre-operative echocardiograms when images were suitable for strain measurement. Pre-operative and follow-up 2 RV strain were compared to that of 43 infants with structurally and functionally normal hearts up to 8 months of age and 8 infants between ages 1 and 4 years, respectively, who were evaluated at our institution and underwent global longitudinal peak systolic RV strain analysis utilizing the same software package.¹³

Global longitudinal peak systolic 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 (MPD) who was blinded to clinical characteristics. Images were obtained on iE33 echo machines (Philips Medical Systems, Andover, MA). Mean frame rates for analysis were 70 ± 17 Hz. To ensure that strain measurements were reproducible, quantification of ten random samples was repeated by a second observer (YW). Systolic strain is represented by negative values, where higher magnitude values represent better myocardial deformation. We defined “worsening” in function as a decrease in the magnitude of strain over time and “improvement” in function as an increase in the magnitude strain.

Clinical data

Data collected included: TOF anatomy (pulmonary stenosis, pulmonary atresia, absent pulmonary valve), gender, age (chronological and corrected gestational, if premature), weight and height at time of repair, neonatal repair (defined as repair within the first month of life), presence or absence of genetic syndromes or other medical comorbidities (e.g. gastro-intestinal malformations or neurologic abnormalities), surgical times (bypass, cross-clamp, and circulatory arrest), type of RVOT intervention (transannular patch or RV to pulmonary artery (PA) conduit), length of intensive care and hospital stay, length of inotropic support, presence of arrhythmia requiring treatment, and number of follow-up catheterizations or surgeries (defined as catheterizations or surgeries to repair residual disease, including residual VSDs, RV outflow tract obstruction, or branch PA stenosis). Intensive care was defined as number of days between surgery and transfer from the intensive care unit to a step-down unit.

Statistical analysis

Descriptive statistics were presented as frequency counts and percentages for categorical variables and mean $\pm$ standard deviation (SD) or median (range or IQR) for continuous variables, as appropriate. Student's t-test was used to compare pre- and post-operative RV strain with normal controls.

Changes in post-operative RV strain over time were investigated using mixed-effects linear regression models implemented via maximum likelihood accounting for correlations arising from the repeated-measures. Using mixed-effects linear regression models, we modeled the between-subject variability as a random effect (random intercept term at the subject level). Mixed-effects models allow use of all data from each subject under the assumption of missing at random. These models examined the relationship of RV strain with time-invariant variables (i.e., length of hospital stay and surgical repair). Analyses were performed by treating time as a categorical variable (pre-operative, post-operative, follow-up 1, and follow-up 2). Univariable analysis for association of RV strain with echocardiogram, TOF anatomy, gender, weight at surgery, neonatal repair, type of repair (including use of ventriculotomy), surgical times (cross-clamp and bypass), length of milrinone therapy, length of intensive care, and length of hospital stay were performed. Potential interaction effects were also explored. Non-significant interaction effects were not included in the final model to achieve a more parsimonious model. Covariates with p-value ≥ 0.2 in the univariable models were included in the multivariable model. Type of surgical repair was kept in the multivariable model regardless of significance. Weight and cardiopulmonary bypass time were not included in the final multivariable model due to collinearity with age at repair and cross-clamp time, respectively. Results from the univariable and multivariable regression models were reported as regression coefficient (changes) with 95% confidence intervals and corresponding p values. A sub-analysis using ANOVA or Kruskal-Wallis test, as appropriate, was performed evaluating differences in TOF anatomy, gender, age and weight at surgery, type of repair (including use of ventriculotomy), surgical times (cross-clamp and bypass), length of milrinone therapy, length of intensive care, and length of hospital stay between subjects in whom strain worsened (defined as decrease in the magnitude of strain by $\geq 1\%$), did not change (increase or decrease in the magnitude of strain by $< 1\%$), and improved (increase in the magnitude of strain by $\geq 1\%$).

An additional sub-analysis including only the 25 subjects who had measurements at pre-operative visit and at least one of the following three visits was also performed. Sensitivity analyses were performed to examine the potential outliers and influential points. These measurements were assessed by visual examination of histograms and normal probability plots of residuals from these models. The two-sided statistical significance level was set at 0.05. All data analysis was performed using STATA 14.1 (StataCorp, College Station, TX).

RESULTS

Ninety-four patients underwent repair for TOF during the study period. Of these, 47 met inclusion criteria. Reasons for exclusion were: three in-hospital deaths, 29 subjects who were followed outside of CHOP, and 15 with inadequate post-operative images for strain measurements.

There was an even distribution of males and females, and the majority of patients had TOF with pulmonary stenosis (62%). The median age of repair was 69 days (interquartile range (IQR) of 6 to 116), with 18 (38%) undergoing neonatal repair. Other characteristics are summarized in Table 1. The average time from surgery to postoperative, follow-up 1, and follow-up 2 echocardiograms were 7 ± 7 days, 8.3 ± 4 months, and 23.2 ± 6 months following repair, respectively.

RV strain was evaluable on most of post-operative, follow-up 1, and follow-up 2 echocardiograms (100%, 91%, and 85%, respectively). For inter-reader reproducibility, intraclass correlation coefficient was 0.93 (IQR 0.17), indicating excellent reproducibility. Strain measurements were possible on all three post-operative echocardiograms in most subjects (37 of 47, or 79%). In 25 subjects (53%), strain was also measured on pre-operative echocardiograms.

There was a significant improvement in RV strain from post-operative to follow-up 1 echocardiograms ($-12.3 \pm 3.3\%$ vs. $-18.8 \pm 2.5\%$, respectively, $p < 0.001$), with no further improvement from follow-up 1 to 2 echocardiograms ($-18.8 \pm 2.5\%$ vs. $-19.8 \pm 3.1\%$, respectively, $p = 0.12$) (Figure 1 and 2). After adjusting for neonatal repair, cross clamp time, length of hospital stay, and surgical repair, changes in RV strain from postoperative to follow-up 1 and 2 remained significant ($p < 0.001$) (Table 2).

Among the 25 subjects with evaluable pre-operative echocardiograms, there was significant worsening in strain from the pre-operative to the early post-operative echocardiograms ($-18.4 \pm 2.9\%$ to $-12.5 \pm 3.6\%$, $p < 0.001$) (Figure 1 and 2). At follow-up 1 and 2, strain was comparable to pre-operative values ($p = 0.93$ and 0.14 , respectively). Pre-operative strain values were not significantly different as compared to normal controls ($-18.4 \pm 2.9\%$ vs $-19.3 \pm 3.8\%$, respectively, $p = 0.3$), though late follow-up strain was significantly worse compared to controls ($-19.8 \pm 3.1\%$ vs $-27.7 \pm 2.8\%$, respectively, $p < 0.001$).

Results from the univariable analyses showed that greater weight at repair and longer cross clamp time were associated with improvement in strain while other factors such as gender, anatomy, type of surgical repair, use of ventriculotomy, bypass time, length of post-operative inotropic support, length of intensive care unit stay, and length of milrinone therapy were not associated with change in post-operative strain. Neonatal repair approached but did not reach statistical significance. The independent predictors of change in strain on the multivariable model were visit, cross clamp time, and length of hospital stay (Table 2). On sub-analysis between subjects in whom strain worsened, improved, or did not change, there was no difference in TOF anatomy ($p = 0.6$), gender ($p = 1$), age and weight at surgery ($p = 0.4$ and 0.8 , respectively), type of repair ($p = 0.8$), use of ventriculotomy ($p = 0.4$), cross-clamp and bypass times ($p = 0.4$ and 0.8 , respectively), length of milrinone therapy ($p = 0.2$), length of intensive care ($p = 0.6$), and length of hospital stay ($p = 0.8$), arrhythmias, ($p = 0.4$), and number of follow-up procedures ($p = 0.6$).

DISCUSSION

Accurate assessment of RV function in patients with TOF is essential, as this population is at increased risk for RV dysfunction and unfavorable outcomes. Mechanisms and risk factors for early dysfunction are not completely understood. In this study, we investigated the changes in RV function in the perioperative and post-operative periods using global longitudinal strain, and the factors associated with such changes. The main findings were that RV strain is comparable to normal controls pre-operatively, worsens early after surgical repair, and recovers to pre-operative values by two years after repair, though it is abnormal compared to controls at two years post-operatively. Longer length of hospital stay is independently associated with worse post-operative strain.

Although preceded by a significant reduction in the early post-operative period, strain improves significantly following surgical repair, indicating the RV's ability to recover from the surgical insult by two years post-operatively. While the changes in RV strain may be a reflection of age-related myocardial changes, strain at conclusion of our study was diminished as compared to normal controls, suggesting that recovery is not solely an age-related phenomenon. A study in children with TOF demonstrated much higher postoperative strain values as compared to pre-operative, not taking into account the change in age 12 months after surgery.¹⁴ Another study in children with TOF repaired at 2.5 years demonstrated that strain worsens at a follow up of 11 years.¹⁵ These conflicting results could be due to younger age at repair and shorter follow-up time in our study; therefore, it is possible that we did not capture potential longitudinal declines in RV function. Alternatively, patients that undergo surgical repair in infancy could have a different trajectory in RV adaptation than those operated at older ages.

Our finding of worse strain at last follow-up as compared to controls is consistent with prior studies.^{14,15} While worse strain in the long-term has been extensively documented,^{1,10,11,16} our findings would suggest that dysfunction begins within the early post-operative years, and may therefore be a direct result of surgical insult. Ye et al posited that pulmonary regurgitation may have a significant effect on early RV dysfunction. However, we could not demonstrate a difference in RV strain based on type of surgical repair, which would refute this argument, as pulmonary regurgitation is less likely to be present early in subjects receiving an RV to pulmonary artery conduit.

Considering that fibrosis is common following TOF repair, the mid-term RV dysfunction may therefore be due to scarring as a result of surgical intervention.¹⁷ Regardless of mechanism, the progression of dysfunction, and risk factors for its development warrant further investigation.

Longer length of hospital stay was independently associated with worsening in myocardial strain. Studies have shown that in the post-operative period, longer intensive care support is associated with restrictive physiology in subjects with TOF.⁵ To our knowledge, the relationship between length of hospital stay and early post-operative RV strain has not been previously demonstrated. These findings suggest that a potentially sick RV impacts early outcome after TOF surgical repair. Thus, TOF patients with longer hospital stays may

represent a high-risk subset of TOF, and therefore may benefit from more careful long-term monitoring.

Greater weight at surgery was associated with strain recovery on univariable analysis. While the benefit of greater pre-operative weight has not been previously demonstrated in this population, this paradigm has been established in infants with single ventricle heart disease, in which low birth weight at the time of repair has been shown to be associated with adverse outcomes.¹⁸ Thus, an alternative hypothesis is that body mass, rather than age, is a more important driving force for RV recovery. While most subjects in our study received milrinone therapy, it was discontinued in the vast majority by 24 hours after surgery, and therefore, we were not able to test an association between length of milrinone and post-operative changes in strain.

Finally, post-operative strain recovery was not associated with ventriculotomy as part of the surgical repair. Myocardial strain was only assessed in the long axis of the RV free wall and septum, and thus deformation of the anterior RV wall, where a ventriculotomy would have occurred, was not evaluated. This may also explain why there was no significant difference based on the type of RVOT intervention, as longitudinal strain would not capture the region of greatest intervention in this group. In previous studies of children and adolescents operated for TOF, RVOT strain is significantly diminished as compared to free wall strain.^{19–21} Further, patients with TOF nearly universally have fibrosis in the RVOT, which may influence RV function.¹⁷ We therefore postulate that the effect of ventriculotomy is likely to be seen locally and impact global ejection fraction, rather than longitudinal strain.²²

These findings may have implications for future clinical care. First, we have demonstrated that RV strain is a reliable and readily obtainable method of measuring RV function in the early post-operative period, and thus may become an important clinical post-operative tool with which to identify and monitor right ventricular dysfunction in the post-operative period. Further, this may open new avenues to identify medical therapies to modify post-operative dysfunction. We have additionally shown that RV strain is normal pre-operatively, but is overall diminished by two years following surgical repair. Long-term RV dysfunction may therefore be an expansion of early post-operative dysfunction, rather than solely due to long-term insults, such as progressive pulmonary regurgitation and RV dilation. Future research is necessary to longitudinally follow this population and identify the progression and additional factors that influence RV dysfunction.

Limitations

This was a retrospective study; therefore we were limited to available echocardiogram images. As such, there were differences in frame rate and machines used for studies, and some measurements were missing secondary to the inability to trace the RV on apical views, especially on pre-operative samples. Though the missingness was accounted for in the mixed effects model, this could have affected our overall power. While the missing data were likely at random due to incomplete images rather than patient characteristics, it is possible that there were intrinsic subject properties that resulted in exclusion. Further, longitudinal strain was only calculated on apical four chamber views; we cannot comment myocardial deformation in the posterior RV or RV outflow tract. This analysis therefore does not

represent global RV strain, but rather longitudinal strain in one plane. Requiring that all patients had follow-up imaging for up to two years limited our analysis to those that survived the post-operative period; as such, we have selected a survival cohort and therefore these results can only be generalizable to that population. RV strain measurements for both controls and subjects were obtained utilizing a TomTec package that was designed for left ventricle analysis; therefore, while our results are internally consistent, these findings may not be externally valid. Finally, this was a single center study, and the results may not be generalizable to all centers due to variations in operative and post-operative management, and age at surgical repair.

CONCLUSIONS

RV global longitudinal strain worsens in the early post-operative period following surgical repair for TOF but recovers through two post-operative years. Despite recovery to pre-operative values, the presence of RV dysfunction as compared to controls at last follow-up suggests that long-term dysfunction may begin early post-operatively. The trajectory of RV dysfunction through the later years therefore needs further study.

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Abbreviations

TOF	Tetralogy of Fallot
RV	Right Ventricle
VSD	Ventricular Septal Defect
IQR	Interquartile Range
RVOT	Right Ventricular Outflow Tract
PA	Pulmonary Artery

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HIGHLIGHTS

- RV strain improves in the first two years following tetralogy of Fallot repair
- Pre-operative RV strain is comparable to normal controls
- Understanding post-operative changes in RV function may inform long-term remodeling

Figure 1.

Right ventricular longitudinal strain by visit. Circles represent actual data points and the bar represents the mean of right ventricular longitudinal strain with 95% confidence interval. P-values represent adjusted results from mixed-effects models. *- results from mixed effects model among the 25 subjects with evaluable pre-operative echocardiograms.

Figure 2. Spaghetti plot of RV strain by visit. Each colored line represents an individual subject, with dots representing each visit.

Table 1

Patient and surgical characteristics.

Gender, Male	24 (51.1%)
Anatomy	
Pulmonary Stenosis	29 (61.7%)
Pulmonary Atresia	16 (34.0%)
Absent Pulmonary Valve	2 (4.3%)
Genetic syndrome	
No	26 (68.4%)
Yes	12 (31.6%)
Age at surgery, days	69 (1 – 640)
Neonate (n=18)	4.5 (1 – 19)
Non-neonate (n=29)	107 (39 – 640)
Weight at surgery, kg	4.2 (2.3 – 9.3)
Neonate (n=18)	3.0 (2.3 – 3.8)
Non-neonate (n=29)	5.7 (2.8 – 9.3)
Surgical repair	
Transannular Patch	43 (91.5%)
RV-PA conduit	4 (8.5%)
RV muscle bundle resection	17 (36.2%)
Pulmonary arteriotomy	18 (38.3%)
Use of Ventriculotomy	19 (40.4%)
Operative course	
Cardiopulmonary bypass time, minutes	63 (25 – 176)
Cross clamp time, minutes	38 (17 – 113)
Bypass runs	

1 run	43 (91.5%)
2–3 runs	4 (8.5%)
Post-operative Course	
Intensive care unit length, days	3 (1 – 39)
Length of hospital stay, days	7 (3 – 65)
Milrinone length, days	1.0 (0.0 – 16)
Arrhythmias, present	22 (46.8%)
Number of follow-up procedures[*]	
None	31 (66.0%)
1	16 (34.0%)

Data are presented as frequency (percentage) or median (range).

RV, Right ventricle; PA, Pulmonary Artery

^{*} Follow up procedures defined as repeat surgeries or post-operative catheterizations

Table 2

Mixed-effects regression models.

n=47	Univariable models		Multivariable model	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Visit				
Follow-up 1 vs. Post-operative	-6.49 (-7.63, -5.35)	<0.001		<0.001
Follow-up 2 vs. Post-operative	-7.45 (-8.62, -6.29)	<0.001		<0.001
Follow-up 2 vs. Follow-up 1	-0.97 (-2.16, 0.22)	0.111		
Cross clamp time, minutes	-0.04 (-0.06, -0.01)	0.006	-0.04 (-0.07, -0.02)	0.001
Cardiopulmonary bypass time, minutes	-0.02 (-0.03, 0.00)	0.069		
	1.16 (-0.04, 2.37)	0.058		
Length of hospital stay, days	0.04 (-0.00, 0.08)	0.082		
Surgical repair			-	-
RV-PA conduit vs. Transannular patch	-0.06 (-2.20, 2.09)	0.959		
Weight at surgery, kg	-0.50 (-0.81, -0.20)	0.001	-	-

Results from mixed-effects regression models are reported as regression coefficient (95% Confidence interval (CI)) with P value. Regression coefficients represent percent change in strain per unit change in covariate.

Age at surgery (neonate vs non-neonate) by visit interactions were not significant, and were not included in the model.

RV, Right ventricle; PA, Pulmonary Artery