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Longitudinal changes in adolescents with TOF: implications for care

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Background We sought to identify predictors of change in right ventricular function and exercise capacity in adolescents following repair for tetralogy of Fallot.

Methods and results We performed a longitudinal study with serial cardiac magnetic resonance imaging and/or exercise stress tests. Patients with interim intervention on the pulmonary valve were excluded. Paired *t*-test was used to detect longitudinal changes and multivariable regression models were built to identify predictors of change. Initial and follow up magnetic resonance and exercise stress test studies were available for 65 and 63 subjects, respectively. Age at initial testing was 11.7 ± 2.7 years. Average follow up time was 4.5 ± 1.8 (magnetic resonance) and 4.0 ± 1.6 (exercise test) years. There was a significant increase in right ventricular end diastolic and systolic volume (119 ± 34 to 128 ± 35 ml/m^2, $P = 0.006$; 49 ± 20 to 56 ± 23 ml/m^2, $P = 0.001$, respectively), and a decrease in right ventricular ejection fraction (60 ± 7 to 56 ± 8%, $P = 0.001$), with no significant change in pulmonary regurgitant fraction or right ventricular cardiac index. Predictors of right ventricular dilation over time included: time elapsed from surgical repair, severity of pulmonary insufficiency and right ventricular dilation at the initial magnetic resonance imaging. Of those, time elapsed from surgical repair had the most significant effect. There was no change in exercise capacity.

Discussion In the adolescent with tetralogy of Fallot, longer time from surgery, more pulmonary insufficiency and greater right ventricular dilation at initial magnetic resonance imaging are associated with progressive right ventricular dilation. These results suggest early monitoring with magnetic resonance imaging might identify those at highest risk for progressive disease.

Keywords tetralogy of Fallot • right ventricle • pulmonary insufficiency • outcome

Introduction

Tetralogy of Fallot is the most common congenital cyanotic heart disease.[1] While early surgical outcomes are excellent in the current era of infant repair, most patients are left with residual lesions including pulmonary insufficiency.[2,3] Pulmonary insufficiency creates a volume load on the right ventricle and is thought to contribute to associated long term complications such as arrhythmias, decreased exercise capacity, right ventricular dilation and dysfunction. As a consequence, many patients experience re-intervention by way of pulmonary valve replacement or reconstruction of the right ventricular outflow tract.[4,5] Indications and optimal timing for pulmonary valve replacement are controversial.[6–10]

To date, relatively few studies describing longitudinal changes in right ventricular function and exercise capacity in the repaired adolescent tetralogy of Fallot population have been performed as compared with numerous retrospective studies that detail outcomes using a cross sectional design.[11–13] In addition, most studies have included patients who were greater than 1 year of age at the time of definitive repair, whose outcomes may not represent those in the

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current era when complete repair routinely occurs during infancy. Thus, changes in cardiac function and exercise capacity that occur during late adolescence in a population following infant repair have not been fully described but are important to detail to define parameters for re-intervention. Moreover, genetic syndromes can also adversely impact outcomes in patients with tetralogy of Fallot. For example, 22q11.2 deletion syndrome is associated with lung disease, worse aerobic capacity, and increased overall morbidity.[14] We therefore sought to describe the course of disease as defined by change in cardiovascular function and exercise capacity in adolescent patients following infant repair of tetralogy of Fallot. We also sought to identify predictors of disease change, including 22q11.2 deletion status.

Subjects and methods

The study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia. We conducted a longitudinal study of patients with initial and follow-up cardiac magnetic resonance imaging studies and/or exercise stress tests. Initial studies were performed as part of a cross-sectional research protocol between 25 January 2005 and 4 May 2009.[15] Patients had complete repair of TOF by 1 year of age [median age of repair 4.8 months (1.2–8.4)] and were 8–18 years at the time of initial enrolment. Early complete repair was defined as repair performed before 1 year of age. All subjects were tested for 22q11.2 deletion syndrome. Those with at least one follow-up cardiac magnetic resonance imaging or exercise stress test between 5 May 2009 and 7 June 2013 were included in the current report. Patients with interim surgical or catheter-based intervention on the pulmonary valve were excluded. Complete repair was defined as a single surgery (with or without a preceding arteriopulmonary shunt) to achieve relief of right-sided outflow tract obstruction and closure of the ventricular septal defect, as compared with a staged repair where multiple surgical procedures preceded closure of the ventricular septal defect. All studies were performed at The Children's Hospital of Philadelphia.

Cardiac magnetic resonance

Cardiac magnetic resonance imaging studies were performed as per our standard protocol, on a 1.5-T Avanto Whole Body Magnetic Resonance System (Siemens Medical Solutions, Erlanghen, Germany), as previously described.[16–18] The protocol includes steady-state, free-precession cine magnetic resonance imaging acquisitions in 4-chamber and long-axis planes and contiguous short-axis cine imaging from the atrioventricular valve level through the apex. All volumes were indexed to body surface area. Phase contrast velocity mapping was performed in the main pulmonary artery to assess pulmonary valve regurgitant fraction. All initial studies were read by a single observer mark Fogel (MF) whereas follow up studies were read by one of four clinical cardiac magnetic resonance imaging attendings (including MF) following a standard protocol from which data were abstracted for the current study. Variables collected included indexed right ventricular end diastolic volume, indexed right ventricular end systolic volume, right ventricular ejection fraction, pulmonary regurgitant fraction, right ventricular mass, right ventricular cardiac index, indexed left ventricular end diastolic volume, indexed left ventricular end systolic volume, left ventricular ejection fraction and left ventricular cardiac index, forward and reverse flow in the aorta and main pulmonary artery. Right ventricular ejection fraction was considered abnormal if less than 45%.[19] Uncorrected stroke volume was calculated by subtracting the end systolic volume from the end diastolic volume. Effective or net stroke volumes were measured by subtracting the reverse stroke volume from the forward stroke volume in the main pulmonary artery and aorta correspondingly.

Exercise stress test

Cardiopulmonary exercise testing was performed per our institution's standard protocol and has been described in detail in previous studies.[17,18] Pulmonary function was evaluated prior to the exercise study using standard methods for spirometry, lung volumes, and conductance as outline by the American Thoracic Society.[20] Forced expiratory volume in one second and forced vital capacity were measured and compared with appropriate reference values.[21] Subjects were exercised to maximal volition using an electronically braked cycle ergometer (SensorMedics, Yorba Linda, CA) per the previously described ramp cycle protocol.[22] Those who were unable to exercise using cycle ergometry used a 1-minute incremental treadmill protocol. Cardiac monitoring was performed using a 12-lead electrocardiogram, blood pressure monitoring, and pulse oximetry. Metabolic data were obtained using a metabolic cart (SensorMedics, Yorba Linda, CA).

Parameters of interest included minute oxygen consumption, oxygen pulse, maximal work rate, maximal heart rate, and respiratory exchange ratio. Ventilatory anaerobic threshold was measured by the V-slope method.[23] Data were compared with healthy age- and sex-matched children using the same exercise protocol as reported by Cooper *et al.*[24] Maximal effort was defined as having achieved a respiratory exchange ratio $>=1.10$.[25]

Electrocardiographic data

The cardiac intervals and rhythm were obtained from review of the most recent electrocardiogram. Electrocardiograms obtained as part of the initial study were available for comparison. .

Clinical data

Clinical variables were queried from the original research database describing the study cohort and included anatomic subtype, genotype status, age at repair, type of surgical repair, and demographic information.[15] Medical records were reviewed for interim interventions, including pulmonary valve replacement or conduit revision, and mortality.

Statistical analysis

Data analyses were conducted in three distinct phases. Normality was tested using the skewness and kurtosis test. First, the subjects with and without follow-up clinical cardiac testing were compared for demographic and clinical factors using a chi-square test or two-sample *T*-test for categorical and continuous variables, respectively. Second, for the patients with follow-up studies, descriptive statistics were reported for initial test value, follow-up test value, and the difference between initial and follow up test values. Paired *t*-tests were used to identify significant changes between initial and follow-up test values. Third, simple linear regressions were used to test the association between each possible predictor and change in cardiac magnetic resonance measurements. Thereafter, in addition to duration of

pulmonary value insufficiency (years), and length of follow up (years), the following predictors were used to generate multivariable models: pulmonary valve anatomy, type of surgical repair, pulmonary valve regurgitant fraction, indexed right ventricular end-diastolic and end-systolic volumes, right ventricular ejection fraction, left ventricular ejection fraction, and presence of end diastolic antegrade flow on the baseline cardiac magnetic resonance study. Multicollinearity for the multivariable models was checked using variance inflation factor. Covariates that were highly correlated were excluded from the multivariable models (e.g., indexed right ventricular end systolic volume was excluded given its correlation with indexed right ventricular end diastolic volume and right ventricular ejection fraction). The independent variables included in the multivariable models were pulmonary valve regurgitant fraction, indexed right ventricular end diastolic volume, right ventricular ejection fraction, left ventricular ejection fraction. The interaction between the initial value and the duration of pulmonary value insufficiency was tested for each model. Significant interaction terms were kept in the final multivariable models. Variables involved in interaction terms were centred in order to overcome multicollinearity.

Results

Initial characteristics

Of 176 subjects enrolled in the original cross sectional study, there were no reported deaths and 92 subjects completed at least one follow-up cardiac study.[15] Two subjects were excluded because of interim interventions. Of the remaining 90 subjects, cardiac magnetic resonance imaging was performed in 65 and exercise stress test in 63; a subset of 38 subjects underwent both cardiac magnetic resonance imaging and exercise stress testing. Since the follow-up cardiac magnetic resonance imaging and exercise stress test were not performed concurrently, we did not conduct comparisons between those tests. The demographics including the mean age at the initial and follow-up testing is provided in *Table 1*. The 22q11.2 deletion status was known for all subjects.

The subset with follow-up cardiac testing was slightly younger at enrolment in the cross-sectional study and was more likely to have undergone repair with a transannular patch. Otherwise there were no statistically significant differences between those with or without follow-up testing with respect to cardiovascular function as described by cardiac magnetic resonance imaging or exercise performance on exercise stress test (*Table 1*).

Change in cardiovascular function by cardiac magnetic resonance imaging

Mean follow up time for cardiac magnetic resonance imaging was 4.5 ($\pm$1.8) years. From the initial test to follow up, there was a significant increase in end-diastolic and end-systolic right ventricular volumes with a corresponding increase in right ventricular stroke volume (*Table 2*). There was a small but significant decrease in right ventricular ejection fraction, though the mean right ventricular ejection fraction remained within normal limits at follow up. Three subjects progressed from normal (initial) to abnormal (follow up) right ventricular ejection fraction, and two subjects had abnormal right ventricular ejection fraction at the initial study and follow up. There was no significant change in pulmonary regurgitant fraction or right ventricular cardiac index. Left ventricular function was unchanged, as defined by ejection fraction and cardiac index, as were left ventricular volumes (*Table 2*). Furthermore, we found no significant differences in right ventricular size and ejection fraction by cardiac magnetic resonance imaging between those with and without a 22q11.2 deletion (data not shown).

Predictors of change in cardiovascular function by cardiac magnetic resonance

We sought to identify variables on the initial cardiac magnetic resonance imaging study that would predict changes seen at follow up.

On multivariable linear regression analysis, we found that time from surgical repair to the initial study, as well as right ventricular dimensions and pulmonary regurgitant fraction from the initial study were associated with progressive right ventricular dilation. Furthermore, the effect of right ventricular dimensions on progressive right ventricular dilation was augmented by the time from repair to the initial cardiac magnetic resonance imaging, as evidenced by the significant *P*-value of the interaction term between initial right ventricular dimension and elapsed time from repair to the initial cardiac magnetic resonance test (*Table 3*). We also found a decline in right ventricular ejection fraction over time, which was associated with longer time from surgical repair, though the initial right ventricular ejection fraction was not itself an independent predictor of further decline in ejection fraction. As before, time from surgical repair to the initial cardiac magnetic resonance imaging augmented the association of initial ejection fraction with further decline in right ventricular ejection fraction. Finally, there was a trend towards greater decline in right ventricular ejection fraction with longer time between the initial and follow up cardiac magnetic resonance imaging (*Table 3*).

In summary, longer time from surgical repair to initial cardiac magnetic resonance imaging exerts the largest effect on progression of right ventricular dimensions and decline in ejection fraction.

Predictors of change in cardiovascular function by exercise stress test

The mean time between initial and follow up exercise stress test was 4 years. Most subjects (50 of 63) underwent exercise stress test using a cycle ergometer. The vast majority of subjects (55 of 63) used the same mode of testing for the initial and follow-up exercise test. There was no significant difference between subjects who underwent testing by ergometer compared with treadmill at initial testing or follow up with respect to percent predicted minute oxygen consumption at peak exercise ($P = 0.12$ and $P = 0.50$, respectively) or the ability to perform at maximal effort ($P = 0.56$ and $P = 0.99$, respectively).

There was significant improvement in the percent of predicted forced vital capacity but no change in: indexed oxygen pulse, percent of predicted oxygen consumption at peak exercise or at ventilatory anaerobic threshold, and in percent of predicted maximal work achieved (*Table 4*).

More patients achieved maximal effort at the follow-up test as compared with the initial study. A subgroup analysis of the 27 patients who performed at maximal effort (respiratory exchange

Table 1 Patient characteristics, cardiovascular function, and exercise capacity at initial testing in those with and without follow-up testing

Variable		No follow up N = 86	Follow up N = 90	P-value
Age of initial study (years)		13.0 (3.4)	11.7 (2.7)	0.02
Gender	Female	35 (41%)	28 (31%)	0.21
	Male	51 (59%)	62 (69%)	
Race	White	74 (86%)	76 (84%)	1.00
	Black	7 (8%)	8 (9%)	
	Other	5 (6%)	6 (7%)	
BSA at MRI (m2)		1.36 (0.33)	1.26 (0.25)	0.054
Subtype of TOF	Stenosis	71 (83%)	64 (71%)	0.32
	Atresia	12 (14%)	17 (19%)	
	Absent pulmonary valve	2 (2%)	7 (8%)	
	With atrioventricular canal defect	1 (1%)	2 (2%)	
Genotype	Non-syndromic	61 (71%)	74 (82%)	
	Trisomy 21	4 (5%)	4 (4%)	
	22q11.2 deletion	18 (21%)	12 (13%)	0.12
	Alagille syndrome	3 (3%)	0 (0%)	
Staged vs. single repair	Complete repair	75 (87%)	72 (80%)	0.24
	Blalock-Taussig shunt to complete	7 (8%)	15 (17%)	
	Staged Repair	4 (5%)	3 (3%)	
Type of surgical repair	Transannular patch	57 (66%)	72 (80%)	0.038
	Non-transannular patch	6 (7%)	7 (8%)	
	Ventricular septal defect closure only	10 (12%)	2 (2%)	
	Right ventricle to pulmonary artery conduit	11 (13%)	9 (10%)	
	Unknown	2 (2%)	0 (0%)	
Cardiovascular function by magnetic resonance imaging				
	Pulmonary valve regurgitant fraction (%)	33 (17)	35 (17)	0.46
	Indexed right ventricular end diastolic volume (ml/m2)	110 (41)	116 (36)	0.36
	Indexed right ventricular end systolic volume (ml/m2)	46 (21)	48 (19)	0.55
	Right ventricular ejection fraction (%)	61 (9)	59 (7)	0.29
	Right ventricular cardiac index (L/min/m^2)	5.4 (1.4)	5.6 (1.5)	0.38
	Left ventricular ejection fraction (%)	69 (8)	69 (7)	0.76
	Left ventricular cardiac index (L/min/m^2)	3.6 (0.8)	3.6 (0.7)	0.78
Exercise capacity				
	Minute oxygen consumption at peak exercise (% of predicted)	76 (19)	76 (17)	0.98
	Minute oxygen consumption at anaerobic threshold (% of predicted)	86 (17)	86 (19)	0.91
	Maximal work rate (% of predicted)	82 (23)	83 (23)	0.78

Values are mean (± standard deviation), percentage, or count (%) where appropriate.
BSA, body surface area; TOF, tetralogy of Fallot; MRI, magnetic resonance imaging.

ratio ≥1.1) on both the initial and follow-up study showed similar results to the entire cohort (*Table 4*).

Electrocardiogram

Most subjects (87%) were in sinus rhythm at follow up. The remaining had ectopic atrial rhythm (11%) while one patient each had ectopic atrial tachycardia and one had idioventricular rhythm. Most subjects had a right bundle branch block (78%) at follow up. These findings were similar to the initial electrocardiogram. We found a significant prolongation of the QRS interval at follow up. There were four subjects at follow up with QRS duration ≥ 180 ms (*Table 2*).

Discussion

We sought to describe predictors of temporal changes in cardiac function in the adolescent population following infant repair of tetralogy of Fallot. Our main findings were that despite a constant pulmonary regurgitant fraction over time, there was an increase in right ventricular size and a decrease in ejection fraction. The strongest effect on progressive right ventricular dilation was time elapsed from repair to the initial cardiac magnetic resonance study, though the severity of pulmonary insufficiency and initial right ventricular dimensions also exert a significant effect. Exercise capacity did not change in the subgroup undergoing a follow-up exercise stress test.

Table 2 Changes in cardiovascular function by cardiac magnetic resonance imaging and exercise capacity over time

	Initial test	Follow up	Difference	*P*-value
Magnetic resonance imaging ($n = 65$)				
Age at magnetic resonance imaging (years)	11.9 (2.8)	16.4 (3.6)	4.5 (1.8)	
Pulmonary valve regurgitant fraction (%)	37 (16)	35 (14)	−1.7 (8.5)	0.13
Indexed right ventricular end diastolic volume (ml/m2)	120 (34)	128 (34)	9 (24)	0.006
Indexed right ventricular end systolic volume (ml/m2)	49 (20)	56 (23)	8 (17)	0.001
Right ventricular ejection fraction (%)	59.9 (7.7)	56.3 (7.8)	−3.6 (8.0)	0.001
Total right ventricular stroke volume (ml)	89.1 (±31)	111 (±31)	+21.9 (±26.4)	<0.001
Indexed effective right ventricular stroke volume (ml/m^2)	41.1 (34.3–48)	42.6 (35.1–49.4)		0.19
Right ventricular cardiac index (L/min/m2)	5.6 (1.5)	5.7 (1.4)	0.1 (1.3)	0.65
Indexed left ventricular end diastolic volume (ml/m2)	65.2 (12.7)	63.4 (11.3)	−1.4 (11.7)	0.37
Indexed left ventricular end systolic volume (ml/m2)	20.6 (6.4)	20.1 (5.7)	0.34 (6)	0.68
Left ventricular ejection fraction (%)	68.8 (6.6)	68.2 (6.2)	−0.6 (6.3)	0.45
Indexed left ventricular stroke volume (ml/m^2)	20.6 (6.3)	20.1 (5.7)	−0.34 (0.82)	0.68
Left ventricular cardiac index (L/min/m2)	3.5 (0.7)	3.5 (0.7)	−0.05 (0.7)	0.59
Exercise stress test (n = 63)				
Age at exercise stress test (years)	11.2 (2.5)	15.2 (2.9)	4 (1.6)	
Minute oxygen consumption at peak exercise (% of predicted)	78 (17)	82 (19)	4 (18)	0.10
Minute oxygen consumption at anaerobic threshold (% of predicted)	86 (19)	90 (19)	4 (18)	0.32
Forced vital capacity (% of predicted)	80 (12)	87 (15)	7 (10)	<0.0001
Maximal work rate (% of predicted)	87 (23)	82 (22)	−5 (18)	0.063
O2 pulse (ml/kg*min)	6.6 (2.3)	11. (3.3)	4.4 (0.42)	<0.0001
Indexed O2 pulse (ml/kg/min/m^2)	5 (1.5)	6.7 (1.9)	1.7 (0.62)	0.17
Maximum heart rate	179 (16)	179 (15)	0 (14)	0.77
Maximal work rate (*n*/%)%	30 (51)	51 (86)		<0.0001
Electrocardiograms ($n = 95$)				
QRS duration	130 (110; 140)	144 (118; 158)	10 (4;20)	<0.0001
Sinus rhythm	81 (90%)	82 (86%)		0.40

Values are mean (± standard deviation), percentage, or count (%) where appropriate.
Maximal work rate (*n*/%)/% indicates the number of subjects that achieved normal work rate.

Though initially well tolerated, severe right ventricular dilation over time has been associated with increased risk of adverse events and currently serves as one indication for pulmonary valve replacement.[19,26] In our study, longer time from surgical repair and a higher pulmonary regurgitant fraction at the time of the initial cardiac magnetic resonance imaging were associated with greater increase in right ventricular volumes, which again suggests that chronic right ventricular volume overload is detrimental over time. In addition, our results suggest that patients with dilated right ventricles are at greater risk of dilating further. Previously described risk factors for more rapid dilation of the right ventricle have included the pulmonary valve regurgitant volume and greater right ventricular end-systolic volume.[8,12,27] Our study demonstrated that severity of pulmonary insufficiency on initial cardiac magnetic resonance correlates with progressive dilation of the right ventricle. Other studies have not reported a similar finding when examining the rate of progression of right ventricular dilation.[13,28,29] On the other hand, and similar to our results, a recent longitudinal report by Wijesekera *et al*[29] demonstrated that in adults with tetralogy of Fallot, rapid rate of progression of right ventricular dilation was associated with larger right ventricular volumes at the time of the initial cardiac magnetic resonance study, thus suggesting that patients with more dilated ventricles at initial studies are at high risk for rapid progression of right ventricular dilation.

In keeping with recent recommendations, our data provide evidence to support initial cardiac magnetic resonance imaging in patients with repaired TOF as they approach adolescence.[30] Such studies would measure right ventricular volumes and pulmonary regurgitation fraction and thereby identify those at risk for more rapid dilation and decline in right ventricular function. Further studies are needed to more accurately define the optimal timing at which to perform initial cardiac magnetic resonance imaging.

We did not find a temporal change in pulmonary regurgitant fraction, similar to other reports that investigated the rate of progression of right ventricular dilation.[12,13,28,29] One possibility is that pulmonary insufficiency is determined early after surgical repair and there is no progression of pulmonary valve insufficiency, but rather, of its effects. An alternative explanation acknowledges that pulmonary valve insufficiency is determined by multiple factors (size of the regurgitant orifice, right ventricular compliance, pulmonary vascular resistance, and heart rate) that may change over time, with the balance of changes causing no net alteration of regurgitant fraction in late childhood and adolescent years.[31]

Table 3 Predictors of change in right ventricular volumes

Dependent variable	Independent variable at initial test	Beta coefficient	Standard error	*P*-value
Change in indexed right ventricular end diastolic volume (ml/m2)	Time from surgical repair (years)	11.34	4.26	0.011
	Pulmonary valve regurgitant fraction	0.76	0.22	0.001
	Indexed right ventricular end diastolic volume	0.73	0.37	0.055
	Interaction between time from surgical repair (years) and indexed right ventricular end diastolic volume	−0.11	0.03	0.002
Change indexed right ventricular end systolic volume (ml/m2)	Time from surgical repair (years)	7.08	3.06	0.025
	Pulmonary valve regurgitant fraction	0.40	0.16	0.014
	Right ventricular end diastolic volume	0.66	0.27	0.017
	Interaction between time from surgical repair (years) and right ventricular end diastolic volume	−0.07	0.02	0.003
Change in right ventricular ejection fraction (%)	Time from surgical repair (years)	7.71	2.68	0.006
	Time of follow up (years)	1.13	0.57	0.053
	Right ventricular ejection fraction (%)	0.67	0.53	0.214
	Interaction between time from surgical repair (years) and right ventricular ejection fraction (%)	−0.12	0.04	0.013

Table 4 Subgroup analysis of patients performing at maximal effort at initial and follow up exercise stress test

Variable	Initial test value	Follow up	Difference	*P*-value
Age at test (years)	12.2 (2.7)	15.9 (3.2)	3.7 (1.6)	
Minute oxygen consumption at peak exercise (% of predicted)	81 (15)	84 (14)	3 (14)	0.36
Minute oxygen consumption at anaerobic threshold (% of predicted)	87 (18)	88 (18)	1 (21)	0.85
Forced vital capacity (% of predicted)	80 (11)	89 (14)	9 (9)	<0.0001
Maximal work rate (% of predicted)	91 (20)	88 (17.33)	−3 (17)	0.43
Indexed oxygen pulse (ml/kg/min/m^2)	5.1 (1.5)	7.7 (1.9)	2.6 (0.62)	0.17
Maximum heart rate	180 (19)	180 (14)	1 (11)	0.69

Values are mean (± standard deviation) or median (IQR).

We found a small but significant decrease in right ventricular ejection fraction, and while the right ventricular ejection fraction remained normal for the entire group, there were a few subjects that progressed from normal to abnormal right ventricular ejection fraction. Others have also found that the right ventricular ejection fraction remained normal over a 5-year follow up of children, adolescents and adults with tetralogy of Fallot.[32] Conversely, Wald *et al*[13], in a study of adults with tetralogy of Fallot demonstrated a significant decline in right ventricular ejection fraction over a median interval of 2 years. This finding suggests that although right ventricular function is maintained for a long time, the right ventricle experiences a decline in function in adulthood and therefore warrants closer surveillance with serial cardiac magnetic resonance studies as patients reach adulthood. Our findings suggest that cardiac magnetic resonance studies should be periodically performed in high-risk patients, such as those with significantly dilated ventricles, moderate-severe pulmonary valve regurgitation and with more time elapsed since surgery at baseline study.

While the study design did not permit testing for associations between cardiac magnetic resonance and exercise stress tests, it is of interest that there was no decrease in exercise capacity in the cohort overall. Surprisingly, percent of predicted forced vital capacity is significantly improved, even though the percent of predicted forced vital capacity remains diminished compared with a normal population. These results do not appear to be secondary to a higher percentage of patients performing at maximal effort, as our subgroup analysis yielded similar results. This observation stands in contrast to a previous longitudinal study, which found a decrease in exercise capacity in a mixed cohort (ages 8–61 years) of patients with repaired tetralogy of Fallot over a 2.7 year follow up period.[11]

Our findings on exercise stress test may in part represent a 'learning curve' seen with repeat exercise testing. However, the long

period of time between tests and similar maximal metabolic data suggest that the improvement is more likely explained by other, as of yet unknown, cardiopulmonary compensatory mechanisms. It has been reported that exercise capacity correlates with habitual exercise in conotruncal anomalies, and it is possible that this subset participated in more habitual exercise over time, which might enhance exercise performance.[33] It is unclear whether or how exercise performance will change in the study cohort over an extended period of follow up, particularly since practitioners may be less inclined to restrict activity in the current day and age.

Finally, we found an interval prolongation in the QRS duration at follow up, although the 75% percentile for both initial and follow up electrocardiograms did not reach the concerning level of 180 ms. The QRS interval is known to prolong over time in patients with tetralogy of Fallot, and the rate of progression in this study appears lower than on previous reports.[32,34] This finding stresses the importance of close follow up of QRS duration since QRS $\geq$ 170 ms is associated with increased risk of death or sustained ventricular tachycardia.[35]

We studied a relatively young population following infant repair. To our knowledge, a similar population has not been described. Previously published longitudinal studies are limited in cohort size, have shorter follow up, include a wide age group, and combine study cohorts with infant and late repairs. As such this study provides an interim evaluation (in between infant and adult age groups) of a more uniform study cohort that may help identify predictors of deleterious change.

Our study is nonetheless limited by its retrospective design even while drawing cases from a single centre and starting from a cross-sectional study cohort. Approximately half of the subjects from the initial cross sectional study did not have follow-up studies at our institution and thus could not be included. However, those with and without available follow-up studies showed no statistical difference in their initial cardiac magnetic resonance and exercise stress test. We were not in a position to compare changes in cardiac magnetic resonance imaging and exercise stress tests in the same patient since the follow-up studies were not performed concurrently with one another.

Larger, longitudinal prospective multicentre studies of an infant tetralogy of Fallot cohort might not only confirm our findings but also provide greater insight in to the dynamic forces following infant tetralogy of Fallot repair.

Conclusions

Our study indicates that pulmonary insufficiency may be determined early after surgical repair and does not progress over time. Moreover, right ventricular volume and ejection fraction as seen on a baseline cardiac magnetic resonance in early adolescence may predict further changes in right ventricular size and function. Additional longitudinal studies starting in the early years after surgery would help determine if pulmonary insufficiency changes over time and may help identify the subset of patients at risk for the most significant adverse right ventricular remodelling. Future studies looking at the impact of habitual exercise on cardiovascular function may also explain differences in exercise capacity. Obtaining a first cardiac resonance study prior to adolescence may help to identify patients at higher risk of decline in function.

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