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Exercise Performance in Tetralogy of Fallot: The Impact of Primary Complete Repair in Infancy

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Abstract. Primary complete repair (PCR) of tetralogy of Fallot (TOF) is now routinely performed in infancy. Although operative results are excellent, the impact on exercise performance is incompletely understood. We reviewed data of all children with TOF who underwent PCR at our institution and had subsequent maximal cycle ergometer exercise testing between January 1995 and December 2000. Of the 193 patients with TOF who underwent PCR, 57 (30%) underwent exercise testing; maximal tests were available for 50 of 57 (88%). Exercise performance of subjects who underwent PCR at <1 year of age was compared to that of those who underwent repair at >1 year of age. The median age at PCR was 10.9 months; 28 subjects (56%) underwent PCR in infancy (<1 year). A transannular incision was employed in the repair in 41 subjects (82%). The mean age at exercise testing was 12.5 ± 3.2 years. The mean maximal VO_2 was 94.9 ± 18.8% predicted and the mean maximal work rate was 98.0 ± 20.8% predicted. In multivariate analysis PCR in infancy (age <1 year) was not associated with maximal VO_2, peak work rate, peak heart rate, or arrhythmias. Only older age at testing and male gender were significantly associated with higher maximal VO_2 ($p = 0.005$ and $p = 0.002$, respectively). Intermediate-term exercise performance in subjects who undergo PCR of TOF in early childhood is near normal. Performing PCR in the first year of life does not impact subsequent exercise performance.

Key words: Exercise testing — Tetralogy of Fallot

Exercise performance following repair or palliation for tetralogy of Fallot (TOF) has been the subject of several investigations [2, 4–7]. In general, these patients have been found to have impaired exercise capacity. The reported aerobic capacity has varied from 68% to 95% of normal [2, 4–7, 22, 23]. A variety of factors have been thought to limit exercise performance in this patient population, including impaired lung function, pulmonary artery distortion, right and left ventricular dysfunction, and chronotropic impairment [6, 15, 23]. During the past 20 years, there has been a trend toward early complete repair of TOF. Most institutions now undertake routine primary complete repair (PCR) within the first year of life and palliative procedures, such as an arterial–pulmonary shunt, are rarely employed [9]. Although early reports of surgical outcome have been encouraging [9, 21], the impact of infant PCR of TOF on subsequent exercise performance is not known. This study reports the cardiopulmonary performance during exercise in a group of children and adolescents following complete repair of TOF with particular attention to those patients undergoing repair in the first year of life.

Methods

Study Population

Patients who underwent PCR of TOF at our institution and had subsequent exercise testing between January 1995 and December 2000 were included in the study. Those subjects with associated absent pulmonary valve, atrioventricular canal, or anomalous coronary artery necessitating placement of a right ventricular to pulmonary artery conduit were not included. During the study period, 214 patients underwent complete repair of TOF at the Children's Hospital of Philadelphia and survived to hospital discharge. There were 21 patients who had complete repair of TOF after initial palliative arterial–pulmonary shunt and were not included in this study. The majority of these patients, 15 of 21 (72%), had palliative surgery performed at another institution. Of the 193 patients who underwent PCR and survived to hospital discharge, 57 (30%) subsequently underwent exercise testing in the Cardiovascular

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Exercise Physiology laboratory between January 1995 and December 2000. Of these patients, 50 (88%) were believed to have achieved a maximal aerobic effort based on metabolic data. This population constituted the study group.

In order to identify factors associated with subsequent exercise performance, medical records were reviewed. Procedure-related factors considered in the analysis included residual lesions, use of a transannular incision, need for reoperation, and year of surgery. In addition, data obtained from subsequent catheterization and/or echocardiography were analyzed. Branch pulmonary artery (PA) stenosis was diagnosed if a >50% luminal diameter narrowing and/or discrete turbulence were visualized echocardiographically at or beyond the bifurcation of the main PA. The degree of pulmonary regurgitation was estimated on the basis of the color Doppler echocardiographic appearance of the regurgitant jet. Right ventricular dilatation was graded in a semiquantitative fashion.

Exercise Testing

Resting Spirometry. Prior to exercise testing, all subjects underwent measurements of resting lung mechanics consisting of inspiratory and expiratory flow volume loops. Maximal volume ventilation was calculated from the forced expiratory volume at 1 second by the following formula: maximal volume ventilation = 40 × forced expiratory volume at 1 second. This value was used to calculate the breathing reserve at peak exercise by the following formula: breathing reserve = [1 – (minute ventilation at peak exercise/maximal volume ventilation)] × 100. The results of the spirometry data were compared to data for healthy children as reported by Polgar and Promadhat [14].

Exercise Protocol. All subjects were exercised to maximal volition using an electronically braked cycle ergometer (Bosch 601). The protocol consisted of 3 minutes of pedaling in an unloaded state followed by a ramp increase in work rate to maximal exercise. The steepness of the ramp protocol was designed to achieve the subjects' predicted peak work rate in 10 to 12 minutes of cycling time.

Cardiac Monitoring. A 12-lead electrocardiogram (Marquette Case-12, Milwaukee, WI, USA) was obtained at rest in the supine, sitting, and standing position. A 12-lead electrocardiogram was obtained during each minute of exercise and during recovery. Cardiac rhythm was monitored continuously throughout the study.

Metabolic Measurements. Metabolic data were obtained throughout the exercise study and for the first 2 minutes of recovery on a breath-by-breath basis using a metabolic cart (SensorMedics, Yorba Linda, CA, USA). Parameters measured included minute oxygen consumption (VO_2), minute carbon dioxide production, minute ventilation, and respiratory exchange ratio. Ventilatory anaerobic threshold was measured by the V-slope method. Data were compared to those of healthy age- and sex-matched children using a similar exercise protocol as reported by Cooper et al.

Statistical Analysis

Continuous variables were summarized as mean values ± standard deviation or median and range, where appropriate. The primary outcome variable was maximal VO_2 scaled allometrically (ml/min/kg$^{2/3}$) [16]. Maximal VO_2 scaled to weight and expressed as percentage predicted are also provided for comparison with other studies. For patients who had undergone more than one exercise study, the most recent study data were used for analysis. Potential predictors of exercise performance were evaluated for their association with maximal VO_2. Age at primary repair was analyzed as a categorical variable (<1 year or >1 year). The data were analyzed with multivariate logistic and linear regression. Analysis was performed with STATA 6.0 (College Station, TX, USA). Significance was determined at a p value of <0.05. All p values are two-sided and confidence intervals are 95%.

Results

Subject Characteristics

Eighteen of the 50 subjects (36%) were female. The median age at complete repair for these 50 patients was 10.9 months (range, 5 days to 5.5 years). There were 28 subjects (56%) who underwent repair before 1 year of age. A transannular incision was employed in 41 subjects (82%). Surgical reintervention after initial repair was required in 6 subjects (12%). These reinterventions included repair of right ventricular outflow obstruction ($n = 2$), resection of right ventricular muscle bundle ($n = 3$), and closure of residual VSD ($n = 1$). Transcatheter balloon dilatation of the pulmonary arteries was performed in 4 (8%) subjects. Patient- and procedure-related variables were compared between the 57 subjects referred for exercise testing and the 136 patients who had primary complete repair, survived to hospital discharge, but did not undergo exercise testing. There was no significant difference between the two groups with respect to age at surgery ($p = 0.73$), use of transannular incision ($p = 0.45$), need for reoperation ($p = 0.10$), or need for transcatheter intervention ($p = 0.24$).

Forty-nine subjects (98%) had echocardiography performed within 1 year of exercise testing. Only 1 subject (2%) demonstrated significant right ventricular outflow obstruction (>30 mmHg gradient). Pulmonary insufficiency (PI) was noted in all but 3 patients. Severe PI was noted in 31 (66%), moderate PI in 9 (18%), and mild PI in 6 (12%). Significant tricuspid insufficiency (moderate or severe) was noted in 3 subjects (6%). Moderate right ventricle (RV) dilatation was noted in 20 (40%) and mild RV dilatation in 16 (32%). No patient was thought to have severe RV dilatation. Significant branch pulmonary artery stenosis was detected in 6 subjects (12%). No subjects had more than mild aortic valve regurgitation.

Exercise and Pulmonary Function Data

The mean age at exercise testing was 12.5 ± 3.2 years. The median interval from PCR to exercise

Table 1. Exercise performance after primary repair of tetralogy of Fallot ($n = 50$).

Variable	Rest (mean ± SD)	Peak exercise (mean ± SD)
Heart rate (bpm)	80.0 ± 12.1	183.2 ± 13.7
FVC (% predicted)	92.1 ± 13.3	
FEV_1 (% predicted)	93.4 ±14.3	
MVV (% predicted)	87.0 ± 33.3	
Systolic BP (mmHg)	104.5± 17.1	144.8 ± 18.3
Diastolic BP (mmHg)	69.4 ± 8.1	68.6 ± 8.2
O_2 saturation (%)	98.1 ± 1.4	96.5 ± 2.1
Work rate (% predicted)		98.0 ± 20.8
VO_2 (ml/min/kg)		39.7 ± 7.6
VO_2 (ml/mm/kg2/3)		145.4 ± 29.3
VO_2(% predicted)		94.9 ± 18.8
Respiratory exchange ratio		1.12 ±. 07
Breathing reserve		25.5 ± 11.4

BP, blood pressure; *FVC*, functional vital capacity; *FEV_1*, forced expiratory volume at 1 second; *MVV*, maximum voluntary ventilation; *O_2*, oxygen uptake.

testing was 11.3 ± 2.9 years. Thirteen subjects (26%) underwent more than one exercise study. The results of exercise testing for the entire cohort are shown in Table 1.

Resting Pulmonary Mechanics. Resting pulmonary mechanics were obtained in 47 subjects (94%) and were within normal range (>80% predicted) for 35 (75%). Eight subjects (17%) had low values for functional vital capacity (FVC) and normal forced expiratory volume at 1 second (FEV_1), suggesting a mild restrictive pulmonary physiology. Three patients (6%) had a borderline FEV_1 and FVC, suggesting a mixed obstructive/restrictive pulmonary physiology. One subject (2%) had normal FVC. but low FEV_1, consistent with obstructive physiology. Age at PCR was not predictive of pulmonary function indices.

Oxygen Consumption. On average, maximal VO_2 was 94.9% of predicted for age and sex. Only eight subjects (16%) had a significantly decreased value (<80% predicted) compared to healthy age-matched data. Early age at PCR was not associated with maximal VO_2 (Table 2). Both older age at exercise testing and male gender were significantly associated with higher maximal VO_2. The relationship between older age at testing did not appear to be related to potential learning curve in patients who had repeat tests. There was also a trend toward lower maximal VO_2 for those subjects with greater RV dilatation as determined by echocardiography. Neither resting pulmonary indices nor peak heart rate were predictive of maximal VO_2.

Physical Working Capacity On average, the study group achieved 98.0% of predicted values for age and sex (Table 1). There were 11 subjects (22%) with maximal work rates below 80% of predicted values. Age at PCR was not associated with maximal work rate (Table 3). As expected, there was a strong correlation between maximal VO_2 and maximal work rate ($r = 0.42$, $p = 0.003$).

Pulmonary Function. Breathing reserve for the entire study group was 25.5% (Table 1). This is within the range previously reported for healthy subjects [11]. Breathing reserve was below 15% in seven subjects (15%). This is the level below which pulmonary capacity potentially impairs aerobic capacity. Breathing reserve was not significantly associated with maximal VO_2 ($p = 0.10$).

Table 2. Predictors of maximal VO_2(ml/min/kg$^{2/3}$)

Patient and procedure-related variables	Coefficient	95% CI	p value
Age <1 year at PCR	−3.82	−22.7–10.8	0.45
Older age at exercise testing[a]	3.64	1.14–6.15	0.005
Female gender	−25.6	−40.8–10.3	0.002
Degree of RV dilatation	−8.9	−19.2–1.38	0.09
Need for reoperation	12.1	−10.5–34.9	0.29
Pulmonary artery stenosis	−3.60	−13.4–6.24	0.47
Degree of pulmonary insufficiency	0.39	−9.01–9.79	0.94

PCR, primary complete repair: *RV*, right ventricle.
[a]Adjusted for effect of repeat studies.

Table 3. Comparison of exercise performance between early and late primary repair

Variable	Age at primary repair <1 year ($n = 28$) (mean ± SD)	Age at primary repair >l year ($n = 22$) (mean ± SD)	p value
Maximal heart rate (bpm)	182.1 ± 14.5	184.6 ± 12.6	0.52
Maximal VO_2 (ml/min/kg)	39.2 ± 6.3	40.8 ± 8.3	0.44
Maximal VO_2 (ml/min/kg$^{2/3}$)	140.3 ± 29.6	152.0 ± 28.3	0.16
Maximal VO_2 (% predicted)	92.3 ± 16.0	99.5 ± 20.2	0.16
Peak work (% predicted)	97.2 ± 23.8	98.9 ± 17.3	0.78
Respiratory exchange ratio	1.10 ± 0.09	1.13 ± 0.10	0.49
FEV_1 (% predicted)	91.8 ± 11.4	95.1 ± 17.0	0.44
FVC (% predicted)	90.6 ± 11.4	93.9 ± 15.3	0.85
Breathing reserve	24.5 ± 11.6	26.7 ± 11.6	0.56

FVC, functional vital capacity; *FEV_1*, forced expiratory volume at 1 second; *O_2*, oxygen uptake.

Cardiac Response. Maximal heart rate averaged 183 beats per minute (bpm), which was 91% of predicted values. Twelve subjects (24%) had impaired chronotropic response with a peak heart rate of less than 180 bpm. Two subjects (4%) had peak heart rates of less than 160 bpm. There was no association between age at PCR and the chronotropic response. Peak heart rate was not associated with maximal VO_2 ($p = 0.62$).

Arrhythmias were noted in 12 subjects (24%). The majority of these patients (10 of 12) had only isolated ventricular or atrial premature beats. Two subjects (4%) had nonsustained ventricular tachycardia during exercise testing. No patient had electrocardiographic evidence of ischemia. Blood pressure response at maximal exercise and maximal arterial oxygen saturation were within the normal range for the study population (Table 1).

Discussion

The influence of age at repair of TOF on later exercise performance has been the subject of several investigations [7, 18, 19, 23]. James and colleagues [7] reported significantly better exercise performance in patients who underwent repair at a younger age. However, the mean age at complete repair in that series was more than 10 years of age. Most centers now employ a strategy of infant repair. Whether this approach improves longer term outcome is a matter of considerable interest. Theoretical advantages to infant PCR include the potential to reduce the adverse impact of cyanosis. In addition, abnormalities of the pulmonary arteries can be addressed early, potentially optimizing long-term growth. One prior study addressed the question of early PCR by comparing exercise performance in those who underwent PCR at <2 years to those who underwent repair at >2 years [18]. Unfortunately, only 4 subjects had maximal studies and metabolic data were not available. Submaximal data suggested that earlier repair did not result in improved work capacity. Similarly, Yetman and colleagues [23] compared exercise performance between those patients undergoing PCR at < 18 months and those undergoing repair at a later age. This series failed to demonstrate any impact of age at repair on exercise, although there were only 10 subjects who underwent PCR in infancy. Singh and colleagues [19] found that 10 patients with TOF who had infant PCR had lower estimated work capacity on treadmill testing than 7 normal controls. In this series the patients with TOF had significant sinus node dysfunction, which appeared to contribute to poorer exercise performance. It is not known how these patients who had infant PCR of TOF compared to subjects who had repair for TOF at a later age.

The current study demonstrates that intermediate-term exercise performance and pulmonary function in subjects who undergo PCR of TOF in early childhood are near normal. Previous studies have generally reported aerobic capacity in the range of 80% of normal. However, the current study failed to demonstrate any significant association between age at PCR and aerobic capacity, peak work rate, or pulmonary function. These data are particularly important when taken in the context of current debate regarding the optimal age for PCR. A recent North American multiinstitutional study reported that the median age for complete repair was 9.0 months, and intermediate palliative shunts were rarely used (8% of patients) [9]. Some centers have even advocated undertaking routine PCR in the first months of life in order to improve pulmonary artery growth and to reduce the volume load on the left ventricle [13].

Although early PCR does not appear to improve exercise performance at intermediate follow-up, the finding that early PCR does not result in later impairment is of clinical importance. There are many other factors that influence long-term outcome and quality of life in patients with TOF. Early repair of congenital heart lesions appears to reduce the risk of embolic events [12]. In addition, prolonged cyanosis— independent of the risk of cerebrovascular accidents—has been associated with adverse neurodevelopmental sequelae in some studies [11]. Early PCR would significantly reduce this risk. If indeed there is no "disadvantage" to early PCR with respect to exercise performance, these other factors may play a more important role in the timing of PCR.

There are theoretical disadvantages of early PCR of TOF. Relief of right ventricular outflow obstruction in a small infant is technically more challenging. As such, a transannular incision may be required in many children. This in turn would result in an increased incidence of PI, which has been found to be a risk factor for right ventricular dysfunction and impaired exercise performance [8, 17]. In addition, Gatzoulis and colleagues [6] demonstrated that restrictive RV physiology, in which there is anterograde flow in the main pulmonary artery during ventricular diastole, is associated with improved exercise capacity later in life. This restrictive physiology is thought to attenuate the adverse impact of chronic PI. In restrictive physiology the RV is relatively noncompliant, which may result in part from the volume and pressure load that occurs in patients with unrepaired TOF. Theoretically, if TOF were repaired very early in life, the development of myocardial fibrosis, and hence restrictive physiology, might not occur and the RV might be more susceptible to progressive dilatation.

It is difficult to analyze the impact of PI in the current study population since the majority of subjects (84%) had at least moderate PI at the time of exercise testing. This is directly related to the use of a transannular incision in most patients. This surgical approach may reflect an institutional bias. Mavroudis et al. [9] reported that in their multiinstitutional study only 30% of patients with uncomplicated TOF had a transannular patch. Despite the high prevalence of PI in our study group, the overall exercise performance was quite encouraging. This suggests that at least in the intermediate term significant PI is not a major determinant of exercise performance. However, it is possible that the prolonged volume load on the RV may lead to further ventricular dilatation and impairment in exercise performance as these patients reach adulthood.

Some authors have suggested that pulmonary artery stenosis is a factor that may impair exercise performance in patients with TOF. Rhodes and colleagues [15] found that peak VO_2 was significantly lower in patients with branch pulmonary artery stenosis diagnosed by echocardiography or radionuclide lung perfusion scan. In that series, 52% of subjects had significant branch pulmonary artery stenosis. In the current study, we were unable to identify branch pulmonary artery stenosis as a risk factor for impaired exercise performance. This may be due to the lower incidence of pulmonary artery stenosis—only six subjects (12%) as defined by the previous criteria. This difference may represent potential selection bias. However, there was no significant difference in the need for transcatheter intervention between those who were referred for exercise testing and those who were not. Alternatively, it may be that the strategy of early primary repair may decrease the risk for development of branch pulmonary stenosis. Data from Alexiou et al. [1] support this hypothesis.

It is interesting to note that older age at exercise testing was associated with higher maximal oxygen consumption normalized for body weight. Mulla and colleagues [10] reported that the maximal VO_2 peaks for females at approximately 12 years of age and for males at 14 years of age. Since the mean age for testing in the current study was 12.5 ± 3.2 years, one would expect to find that older age might be associated with lower maximal VO_2. Instead, we found that older patients achieved a higher maximal VO_2. It is possible that older patients might have been tested previously and thus do better on that basis. However, we adjusted for the effect of repeat testing in the multivariate analysis. Despite the encouraging association of higher maximal VO_2 in older subjects in our series, we recognize that these patients must be followed closely because most previous studies have suggested that RV dilatation is likely to progress and exercise function may deteriorate in some patients as they reach adulthood [20].

The major limitation to this study is that less than one-third of the children who survived PCR of TOF underwent exercise testing. This is due to the fact that many patients in this series did not receive long-term care at our institution. In addition, there is considerable variability in the use of exercise testing among cardiologists. Although the potential selection bias is significant, the study population appeared to be representative at least with respect to several important demographic and operative variables. Additionally, the age at which patients undergo PCR is undoubtedly influenced by a variety of factors, including degree of right ventricular outflow obstruction. It is difficult to account for such bias in the retrospective study design.

Conclusions

The findings of this study demonstrate that at intermediate follow-up cardiopulmonary performance during exercise following PCR of TOF is near normal. Repair in the first year of life does impact intermediate-term exercise performance. Longer term follow-up of this cohort of patients, with particular attention to the impact of PI, is required.

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