Cardiol Young 2002; 12: 554–559

ISSN 1047-9511

Original Article

Aerobic capacity in adults with tetralogy of Fallot

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Abstract *Background:* We investigated the aerobic capacity of 168 adult patients who had undergone successful surgical repair of tetralogy of Fallot at the University of Toronto Congenital Cardiac Centre for Adults. *Methods:* We compared values of peak uptake of oxygen, peak heart rate, forced vital capacity, and forced expiratory volume in 1 second to predicted values for their age groups. *Results:* The patients who had undergone surgical repair of tetralogy of Fallot demonstrated an overall diminished peak uptake of oxygen, at 51%, and peak heart rate, at 79%, compared to predicted values. No difference in peak aerobic capacity was found according to the initial surgical strategy of palliation or repair. *Conclusions:* Adult patients who have undergone surgical repair of tetralogy of Fallot have lower peak uptake of oxygen, and peak heart rate, compared to predicted values. The reduction in the peak heart rate may affect their exercise capacity. The peak uptake of oxygen also decreased with increasing age at the time of testing, and the age at surgical repair.

Keywords: Congenital heart disease; cardiopulmonary test; spirometry

Tetralogy of Fallot is the most common cyanotic congenital cardiac malformation, with an incidence of 0.1 in every 1000 live births.[1] The natural history of the condition was grim prior to surgical intervention, with almost half the patients dying by the end of the first year of life.[2] In the 1940s, palliative surgery was introduced by Blalock and Taussig that changed survival dramatically.[3] Surgical repair consists of closure of the ventricular septal defect and reconstruction of the right ventricular outflow tract. The latter procedure often leads to pulmonary insufficiency, with right ventricular volume overload and dysfunction as a result.[4–7] Pulmonary valvar insufficiency is usually well tolerated in the medium-term, but in the longer term it may result in increasing exertional fatigue, dyspnea, arrhythmias, cardiac failure, and sudden death.[5,7–9] Pulmonary valvar replacement is often the solution, and this procedure has been shown to provide clinical improvement and a reduction of right ventricular volume overload.[5] The most commonly used variable to describe aerobic capacity is the peak uptake of oxygen. On average, the peak uptake has been reported to be moderately reduced compared to predicted values.[10] As far as we are aware, however, no studies to date have addressed lung volumes and aerobic capacity in the different age groups of an adult population which has undergone surgical repair of tetralogy of Fallot.

The aim of our study, therefore, was to explore the differences between reference values of a healthy adult population and very late follow-up of one of the largest cohorts of patient in North America with repaired tetralogy of Fallot with respect to lung function and dynamic exercise data.

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Accepted for publication 12 July 2002

Methods

Patients

In this retrospective study, we identified patients with repaired tetralogy of Fallot were in the database of the

https://doi.org/10.1017/S1047951102001002 Published online by Cambridge University Press

Table 1. The patients undergoing surgical repair of tetralogy of Fallot entered in the database of the University of Toronto-Congenital Cardiac Centre for Adults.

Total number with Tetralogy of Fallot	n = 494
Late mortality >18 years	n = 35 (7%)
Lost to follow-up	n = 87 (18%)
Patients followed actively	n = 372 (75%)
Patients with cardiopulmonary test	n = 168 (45% of patients followed actively)
Males/Females	n = 87/81
Age at testing (years)	median age = 32 (19–64)
Age at surgery (years)	median age = 7 (1–55)
Years since repair (years)	median age = 23 (1–41)
Type of initial repair	n = 93 Transjunctional patch
	n = 15 Pulmonary valvotomy
	n = 15 Infundibular resection
	n = 14 External conduit
	n = 10 Arterioplasty

Data is shown with the median and range.

University of Toronto Congenital Cardiac Centre for Adults. The population, with its descriptive data is displayed in Table 1. These patients were members of the group regularly followed in the clinic, not all of whom had had their exercise tests by the time data collection had closed. Other patients were no longer under active follow-up, usually because of death, non-compliance, or geographic factors. The cardiopulmonary data have been assessed over a 10-year period from 1989 to 1999. In cases with more than one test performed, the last test was selected.

The criterions for replacement of the pulmonary valve at the University of Toronto Congenital Cardiac Centre for Adults includes symptoms that limit activity of daily living attributable to right ventricular dysfunction, sustained atrial or ventricular arrhythmia, and progressive right ventricular dysfunction and dilation, as assessed with a combination of echocardiography, angiography, radionucleide angiography, or magnetic resonance imaging, in association with severe pulmonary regurgitation. The latter is determined by echocardiography, by magnetic resonance imaging showing a reduction of greater than 20% in the pulmonary regurgitant fraction, or angiographically. Of the 38 patients in whom the pulmonary valve had been replaced, it was replaced in 32 (80%) before the age of 25 (Table 2). The patients with moderate-to-severe pulmonary regurgitation were under constant consideration for replacement of the valve, but the repair had not yet been performed.

Cardiopulmonary testing

On an ergometer cycle (Elema, Solna, Sweden), continuous measurements of expired gas values were analysed every 30 s using an Amtech VO_2 Oxygen Analyser S-3A/I, Pittsburgh, Pennsylvania, United

Table 2. Type of additional repair (n = and % of total).

Blalock-Taussig shunt	76 (45.2%) (34 left shunt, 42 right shunt)
Waterston shunt	9 (5.3%)
Pott's shunt	1 (0.6%)
Aortic valvar replacement	7 (4.1%)
Resection of outflow tract aneurysm	9 (5.3%)
Tricuspid valvar replacement or annuloplasty	10 (5.9%)
Mitral valvar repair	1 (0.6%)
Atrial septal defect closure	13 (7.7%)
Conduit from right ventricle to pulmonary arteries	3 (1.8%)
Balloon dilation of pulmonary trunk	4 (2.4%)
Patch enlargement of pulmonary trunk	3 (1.8%)
Branch pulmonary arterioplasty	15 (8.9%)
Palliative infundibulectomy	2 (1.2%)
Pacemaker	6 (3.6%)
Cryoablation	8 (4.8%)
Pulmonary valvar replacement (total)	38 (22.6%)
Type of valve	(% of pulmonary valvar replacement)
Porcine	27 (71.1%) (Hancock, Medtronic or Carpenter-Edwards)
Pericardial	11 (28.9%) (Ionescu-Shiley or Symbion)

States of America. The analyser was calibrated prior to making tests using known values of oxygen and carbon dioxide. During the tests, measurements of blood pressure, the electrocardiogram, and saturation of oxygen were recorded continuously. All patients started a 1-minute warm-up at 20 W. Workload was increased by 20 W every 2 min to fatigue. We used the guidelines of the American College of Sport Medicine for ending the cardiopulmonary test.[11] Prior to exercise, spirometry tests were conducted with measurements of forced expiratory volume in 1 s and forced vital capacity, using the equipment of SensorMedics, Yorba Linda, California, United States of America.

The results of peak uptake of oxygen in the patients were compared with a healthy population in Canada for the corresponding age groups.[12] The results for forced expiratory volume in 1 s, forced vital capacity, and peak heart rate were compared to predicted values calculated from equations given by Jones and Trumbold.[13]

Statistics

Data were analysed using Statistical Package of Social Science 9.0 for Windows. Median values of peak uptake of oxygen were calculated for the whole group of patients undergoing surgical repair of tetralogy of Fallot so as to make comparisons with those of a healthy population. Differences between the results in the repaired patients and the predicted values with respect to forced vital capacity and forced expiratory volume in 1 s were analysed with the Mann-Whitney

Table 3. Cardiopulmonary results (mean ± standard deviation) for the patients as a group, and divided into gender.

Variable	All patients	Male	Female	p value
Peak oxygen uptake (millilitres kilo^{-1} minute^{-1})	21.1 (±7.2)	23.8 (±7.41)	18.2 (±5.8)	<0.0001
Peak oxygen uptake (millilitres minute^{-1})	1414 (±551)	1693 (±558)	1114 (±350)	<0.0001
Peak ventilation (litre minute^{-1})	53.6 (±19.2)	62.6 (±19.9)	44.2 (12.8)	<0.0001
Peak heart rate (beat minute^{-1})	149 (±27)	155 (±22)	142 (±31)	0.003
Respiratory exchange ratio	1.11 (±0.10)	1.11 (±0.10)	1.11 (±0.10)	0.731
Oxygen-saturation (%)*	94 (±3)	94 (±3)	94 (±4)	0.833
Forced vital capacity (litre min^{-1})	3.45 (±1.00)	3.97 (±0.95)	2.89 (±0.72)	<0.0001
Forced vital capacity (% predicted)	84 (±17)	85 (±17)	84 (±17)	0.889
Forced expiratory volume in 1 s (litre minute^{-1})	2.82 (±0.82)	3.22 (±0.78)	2.38 (±0.62)	<0.0001
Forced expiratory volume in 1 s (% predicted)	86 (±22)	86 (±22)	86 (±22)	0.991

The p values indicate the gender differences; *The data for oxygen-saturation is at exercise termination and is lacking for 15 patients.

test. Analysis of variance was used to assess differences according to age groups, type of repair, and severity of pulmonary regurgitation, using the method of Bonferroni. Multivariate linear regression modeling with the stepwise backward elimination selection procedure was used to examine the relationship between age at repair, age at test, years since repair, pulmonary valvar replacement, gender, heart rate, original surgical method, and the degree of pulmonary regurgitation for the variable peak uptake of oxygen. If two independent variables were correlated ($r > 0.70$), only the variable with the strongest correlation with the outcome of interest was entered into the multivariate model. A p value <0.05 was regarded as statistically significant.

Results

Cardiopulmonary testing

The mean values from the cardiopulmonary tests are listed in Table 3. Mean peak uptake of oxygen in milliliters per kilo^{-1} per minute^{-1} in the patients undergoing surgical repair was severely diminished compared to healthy subjects of the same age (Fig. 1). The slope of the fall-off across age groups with respect to peak uptake of oxygen in the patients who had undergone surgical repair ($p < 0.0001$) was similar to healthy subjects (Fig. 1). No effect with regard to peak uptake of oxygen was detected according to the type of initial surgical repair ($p = 0.984$, Fig. 2). In some patients who had received a new pulmonary valve, there was pulmonary regurgitation, but with no impact on peak uptake of oxygen ($p = 0.553$). In addition, no difference was found between patients in whom the pulmonary valve had been replaced with regard to peak uptake of oxygen ($p = 0.811$).

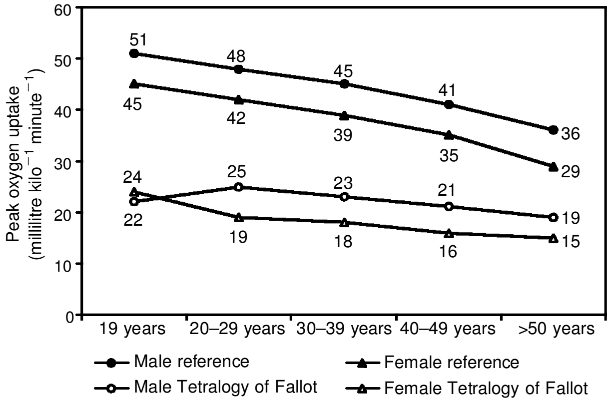

Figure 1.
The peak uptake of oxygen, in millilitres kilo^{-1} minute^{-1}, for the 168 patients who had undergone surgical repair of tetralogy of Fallot is compared to a healthy population (17). The values for patients are given in median and 75th centile for both sexes in order to compare with the reference population (median & 25th centile). The age groups are up to 19 years, comprising 3 males and 4 females, from 20 to 29 years, with 38 males and 25 females, from 30 to 39 years, with 23 males and 27 females, from 40 to 49 years, with 16 males and 14 females, and older than 50 years, comprising 6 males and 11 females.

Patients in whom the pulmonary valve had not been replaced, however, showed significantly more variation ($p = 0.002$) between the groups of "none", "mild", "moderate" and "severe" regurgitation, with the lowest peak uptake found in patients with mild regurgitation (Fig. 3).

With regard to peak heart rate, the values were diminished in those undergoing surgical repair, with higher values for males (Table 3). The mean values of the ratio of respiratory exchange indicate that the patients achieved near maximal values, and there were no significant drops in saturation (Table 3).

https://doi.org/10.1017/S1047951102001002 Published online by Cambridge University Press

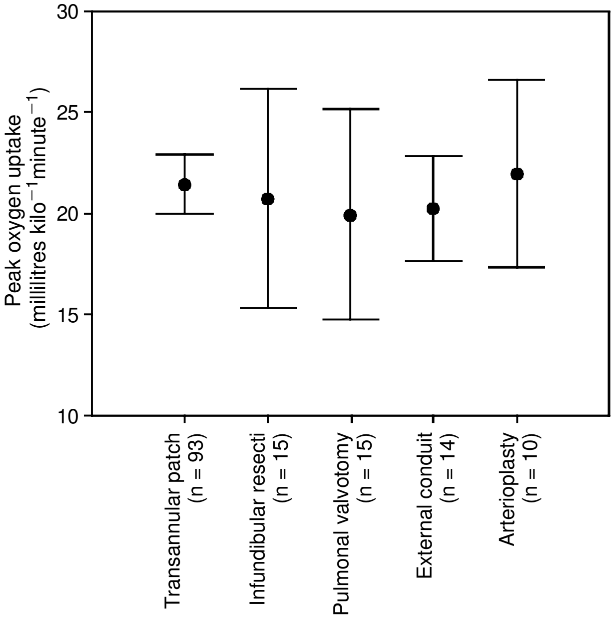

Figure 2.
The impact of the initial surgical method on peak uptake of oxygen. The data were available from 147 patients, one having had a different method, and 19 having missing data due to operation abroad.

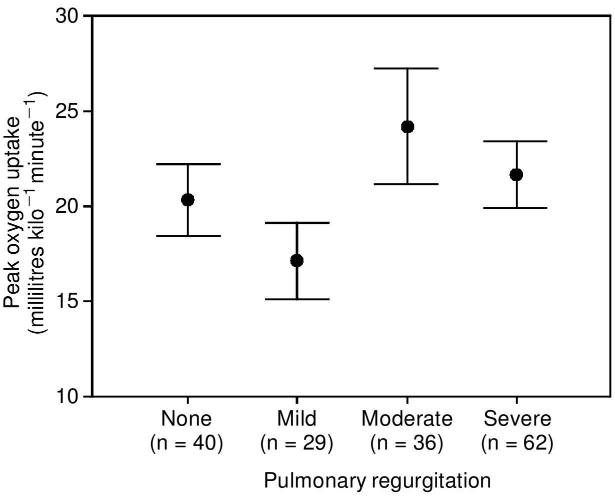

Figure 3.
The effect of pulmonary regurgitation on peak uptake of oxygen for patients in whom the pulmonary valve had not been replaced.

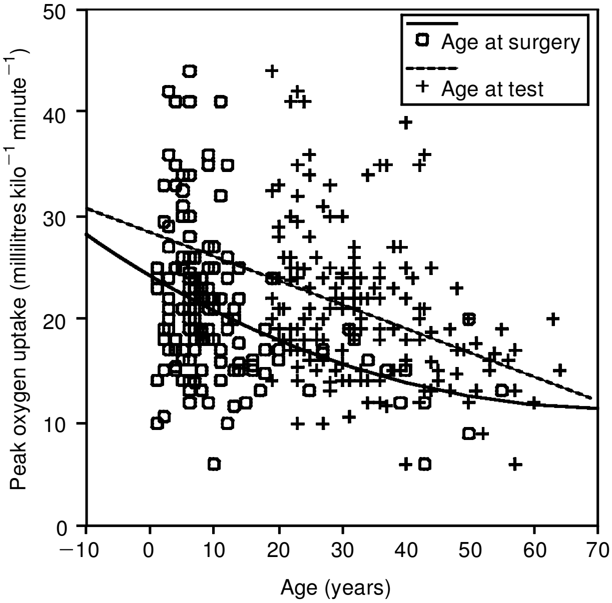

Figure 4.
The effect of age at repair, and age at testing, on the peak uptake of oxygen, based on data from 165 patients. Information was lacking on age at repair in 3 patients).

In the multivariate linear regression model, age at repair, peak heart rate, gender and the absence of replacement of the pulmonary valve all had a significant positive impact on the peak uptake of oxygen uptake. There was a correlation between age at test and age at surgery ($r = 0.72$, $p < 0.0001$). Using our criterions then excluded age at test in the regression model (Fig. 4). Male patients achieved higher values ($p < 0.0001$, Fig. 1), and younger age at repair conferred a beneficial effect on peak uptake of oxygen ($p < 0.001$, Fig. 4). Also, the older the patients were at test, the lower were the values for peak uptake of oxygen ($p < 0.001$, Fig. 4). There was an overall positive relationship between high heart rates and high values of peak uptake of oxygen ($r = 0.53$, $p < 0.0001$).

Lung function

There was a significant difference between predicted values and obtained values both for forced vital capacity ($p < 0.0001$) and forced expiratory volume in 1 s ($p < 0.0001$) in the patients who had undergone surgical repair, although the mean results were above 80% of predicted. A correlation was found between peak uptake of oxygen and both forced vital capacity ($r = 0.59$, $p < 0.01$) and forced expiratory volume in 1 s ($r = 0.61$, $p < 0.01$).

Discussion

Our retrospective study has shown that adults who have undergone surgical repair of tetralogy of Fallot have lower aerobic capacity than their peers, partly due to reduced peak heart rate. Both age at test, and age at surgery, had an impact on the aerobic capacity. The lung volumes in the patients are also reduced compared to predicted values, but are within 80% of normal, which is considered as the threshold for having any impact on aerobic capacity.

Aerobic capacity

In agreement with most previous reports,[5,9,14–18] we found that the patients undergoing surgical repair had impaired peak uptake of oxygen compared to healthy subjects, although Clark et al.[19] had showed near normal exercise capacity in their cohort. The cause of impairment is probably multifactorial and may, as suggested by others, partly relate to the degree of pulmonary regurgitation and right ventricular dysfunction.[5,10] From this lower initial performance, the patients follow the natural decline with age in peak uptake of oxygen. The consequence may be that heart failure occurs at an early age. This demands a close follow-up by a specialised cardiologist, and indicates a need for qualified programs of health care to follow these patients.

There is a strong correlation between the age at testing and the age at surgery in the present data. Patients who had their repair at a young age, below the age of 10 years, also had their tests at a younger age, below the age of 35 years. Patients repaired before the age of 10 years have a much better peak uptake of oxygen than those repaired at an older age. This is in agreement with the findings of Bjarke and colleagues.[20] Rowe et al.,[15] however, found no correlation between age at surgery and exercise capacity in patients repaired prior to the age of 11. This suggests that the variables of age at testing and age at surgical repair must be taken into consideration when analyzing the data. In our present multivariate linear regression model, we took account of both age at testing and age at surgical repair.

The peak values for uptake of oxygen in our study, however, are much lower than those reported by others.[10] This may partly be explained by the fact that our patients were older. Thus, the mean age of the patients studied by Wessel et al.[10] was 17.1, with a standard deviation of ±7.4, as opposed to 33.2, with standard deviation of ±10.6, for our patients. The extent of follow-up after repair were also considerably longer in our study, at 22.7 years, with a standard deviation of ±7.6 years, as opposed to 9.6 years with a standard deviation of ±5.3 years in the study of Wessel and colleagues.[10] Also, the differences between the healthy population and the patients were bigger in our present study. This may be explained by the fact that our reference values are based on 23,000 healthy Canadians, who may have a higher daily level of activity, and therefore higher median values, than other reference populations in North America.

The peak heart rate achieved by the repaired patients in our study was severely reduced compared to their healthy controls.[21] The ratio of obtained to predicted peak heart rate showed a mean value of 79%, with a standard deviation of ±14%, compared to earlier reports of 94%, with a standard deviation of ±7%.[15] The diminished peak heart rate may in part explain the inability of our patients to achieve normal uptake of oxygen.

A subgroup analysis, using analysis of variance, of patients in whom the pulmonary valve had not been replaced indicated that those with none or mild pulmonary regurgitation had lower peak uptake of oxygen when compared to those with moderate and severe pulmonary regurgitation. The explanation for the lower values is that those patients with none or mild regurgitation were older when tested, and older at the time of surgical repair, than the patients with more severe pulmonary regurgitation. Interestingly, no difference was found based upon the type of initial repair, be that by so-called transannular patching, in which the patch is placed across the anatomical ventriculo-pulmonary junction, insertion of an external conduit, pulmonary arterioplasty, pulmonary valvotomy, or infundibular resection.

Lung function

Our patients had reduced forced vital capacity, at 82 to 88% of predicted values, across the different age groups, a finding in accordance with previous reports.[10,22] Wessel et al.[10] suggested that hypoplastic lungs, altered chest wall movement due to pulmonary vascular changes, and lack of physical activity all contributed to the diminished lung volumes in patients with tetralogy of Fallot. Sternotomy may also reduce both lung function and lung volumes.

Limitations of the study

No information is available for patients not followed actively by the clinic. Our retrospective study may therefore be biased towards the more symptomatic patients. It would be of interest to perform sub-group analysis before and after late re-operation, after pulmonary valvar replacement, and in those with pulmonary stenosis. Unfortunately, these data are not available. The retrospective nature of the study may also have introduced a selection bias in the patients studied.

Conclusion

We have confirmed that adults, after surgical repair of tetralogy of Fallot, have lower peak uptake of oxygen, lower forced vital capacity, lower forced expiratory volume in 1 s, and lower peak heart rate compared to healthy subjects. The reduced peak heart rate may affect their aerobic capacity. The technique of initial surgical repair, and the severity of persisting pulmonary regurgitation, did not seem to affect the results. Age at repair, age at testing, and the period since surgery, all had an impact on the results. The age at surgical repair was an important predictor of exercise capacity, as patients repaired at a younger age achieved greater peak uptake of oxygen.

Acknowledgements

Dr Fredriksen is supported by the Norwegian Association for Children with Congenital Heart Disorder, The Norwegian Lung and Heart Association, and The National Foundation of Public Health in Norway. Dr Veldtman is supported by the National Heart Research Fund, United Kingdom.

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