ORIGINAL RESEARCH

Exercise capacity of children with pediatric lung disease

G.S. Zavorsky^{1,2}

J.R. Kryder¹

S.V. Jacob⁵

A.L. Coates⁴

G.M. Davis³

L.C. Lands³

¹ Department of Obstetrics, Gynecology, and Women's Health, Saint Louis University, Saint Louis, MO, USA

² Department of Pharmacological and Physiological Science, Saint Louis University, Saint Louis, MO, USA

³ Division of Respiratory Medicine, Montreal Children's Hospital – McGill University, Montreal, Canada

⁴ The Hospital for Sick Children – University of Toronto, Toronto, Canada

⁵ Hôpital Ste-Justine, Montreal, Canada

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Abstract

Background: Pulmonary function of children with cystic fibrosis (CF) and bronchopulmonary dysplasia (BPD) is similar at rest even though the mechanisms of injury differ. We sought to compare the peak exercise responses in children with BPD versus CF while controlling for pulmonary impairment, nutritional status, gender, age, height, and predicted forced expired volume in 1 second (~73% of predicted).

Methods: Nine BPD children and 9 CF children underwent spirometry and a progressive exercise test to maximum on a cycle ergometer.

Results: There was no difference between groups in body mass percentile (CF: $97 \pm 13\%$, BPD: $98 \pm 11\%$), peak power output (W_{peak}) (CF: 67 ± 19 W, BPD: 73 ± 28 W), % predicted W_{peak} (CF: $83 \pm 28\%$, BPD: $88 \pm 15\%$), peak oxygen uptake (VO_{2peak}, CF: 38 ± 7 ml/kg/min, BPD: 39 ± 6 ml/kg/min), or % predicted VO_{2peak} (CF: $99 \pm 16\%$, BPD: $96 \pm 27\%$).

Conclusions: Children with mild pulmonary impairments are able to achieve a near normal peak power output and a

normal VO_{2peak}. Neither the aetiology nor the developmental onset of the process appears to be important influences on VO_{2peak} or W_{peak}.

Both cystic fibrosis (CF) and bronchopulmonary dysplasia (BPD) are common chronic childhood conditions that are characterized by chronic airflow limitation and hyperinflation of the lungs, resulting in a mixed obstructive/restrictive pulmonary disease. The lung disease of cystic fibrosis results from a progressive inflammatory process associated with chronic low grade infection, leading to bronchiectasis and progressive destruction of lung parenchyma.¹ Accordingly, patients with cystic fibrosis typically have high levels of circulating immunoglobulins, elevated sedimentation rates, and other indices of continuing inflammation. In contrast, bronchopulmonary dysplasia is characteristically

seen following prolonged positive pressure ventilation and high inspired oxygen concentration during infancy, leading to a parenchymal injury with incomplete repair by the inflammatory process. Thus, bronchopulmonary dysplasia is the result of an early inflammatory response with distortion of lung architecture typified by areas of over-distension adjacent to areas of fibrosis.² This inflammatory process is, however, believed to be circumscribed and limited to the period of ventilatory and supplemental oxygen support because, on long term follow-up, there is no evidence of ongoing inflammation.³ Also, while there is frequently an intestinal malabsorptive problem in cystic fibrosis patients, this abnormality is not a feature of bronchopulmonary dysplasia.

Another important difference is that bronchopulmonary dysplasia (also called chronic lung disease of infancy or CLD) patients often have pulmonary hypertension and right ventricular hypertrophy at an early age.⁴ Although there may be incomplete repair of the early lung disease by active remodelling of alveolar-capillary gas exchange units⁵, the obvious signs of pulmonary hypertension typically resolve in the first two years of life with careful attention to ensuring adequate oxygenation.⁶ In contrast, pulmonary hypertension and cor pulmonale is a late finding in cystic fibrosis, and is associated with severe airflow limitation and the development of hypoxemia.

Several cross-sectional studies in patients with cystic fibrosis have demonstrated that both poor nutritional status and abnormal spirometry affect the exercise capacity (peak oxygen uptake or $\text{VO}_{2\text{peak}}$ measured in ml/kg/min and L/min) of these patients.⁷⁻¹¹ Longitudinal data also suggest that pulmonary function (i.e. forced expiratory volume in 1 second) is correlated with exercise capacity in those with cystic fibrosis.¹² Studies of exercise capacity in older¹³⁻¹⁵ and younger^{15,16} children with a spectrum of severity of bronchopulmonary dysplasia have generally demonstrated that, despite reductions in lung function, many patients can achieve an exercise capacity within or slightly below the normal range. Other studies¹⁷⁻¹⁹ have reported diminished ex-

ercise capacities in patients with a history of relatively mild bronchopulmonary dysplasia. The reasons for these discrepant results are not clear.

While the spirometric abnormalities of pulmonary function are similar at rest, the mechanisms of injury differ markedly and differences in gas exchange function during exertion may occur. Thus, we sought to compare the exercise responses of children, with either cystic fibrosis or bronchopulmonary dysplasia, matched for sex, age, height, and lung function, to determine whether there were differences in peak oxygen uptake or peak power output (W_{peak} , measured in watts). We hypothesized that there would be differences in ventilatory responses that would become evident upon maximal exercise.

Materials and Methods

Study design

In a post-hoc analysis of patients recruited from the hospital for exercise testing, patients from the two groups were matched for sex, age, height, and FEV_1 predicted. We studied nine matched pairs of subjects: three male pairs and six female pairs. Only 3 of 9 cystic fibrosis patients had any previous experience performing an exercise test. The bronchopulmonary dysplasia patients were a subgroup of long term follow-up study of infants with severe bronchopulmonary dysplasia (which we defined as those who required supplemental oxygen at 44 weeks post-conceptual age).¹⁵ Inclusion criteria for bronchopulmonary dysplasia were: (1) premature birth at 34 weeks gestational age or less, (2) clinical and radiological diagnosis of bronchopulmonary dysplasia, (3) requirement for supplemental oxygen for at least 1 month post-term, (4) discharge to home supplementation. The inclusion criteria for cystic fibrosis included a positive sweat chloride test ($> 60 \text{ mmol/L}$) and typical pulmonary and gastrointestinal symptoms compatible with cystic fibrosis. Exclusion criteria for both groups were: (1) congenital heart disease other than patent ductus arteriosus, (2) ongoing oxygen need

related to a primary respiratory diagnosis other than bronchopulmonary dysplasia and cystic fibrosis, (4) pulmonary hypertension, and (4) inability to participate in pulmonary function / exercise testing because of the presence of a tracheostomy or severe neurologic impairment.

Methods

Institutional review board approval was obtained before recruitment of patients. All patients were weighed on an electronic balance, and had standing height measured by stadiometer. The nutritional status of each child was expressed as body mass percentile⁸, which is the body mass index (weight/height²) expressed as a percentage ideal body mass index of a child of the same sex and age growing at the 50th percentile according to the normal values determined by the National Centre for Health Statistics. Lung function was measured by spirometry and expressed as a percentage of predicted normal values.²⁰

Peak power output was determined from a maximal progressive test performed on an electronically braked cycle ergometer. The test consisted of incremental changes in work load, based on height and sex of the subject, at one minute intervals. The exercise protocol is designed so that exhaustion (inability to maintain pedalling velocity at 60 rpm against a known work load) will occur between 5-10 min after the start of the study, with the maximum workload being the last workload sustained for a full minute at a pedalling speed of 60 rpm. Peak power output was expressed as the percentage of predicted, based upon gender and height.²¹ Peak oxygen uptake, defined as the average of three highest 20 sec VO₂ averaged intervals, was expressed as a percentage of predicted values based on sex and height by Cooper and Weiler-Ravell²². Predicted peak heart rate was defined as 220 – age, and predicted O₂pulse at peak exercise was defined as 0.28*height in cm – 3.3*sex – 26.7, with male = 0 female = 1²³. As detailed in the previous publications cited above, ventilation was measured by a dry gas meter (Parkinson-Cowan) on the inspiratory

line, while exhaled gas was exhausted through a variable volume mixing chamber, with the volume adjusted to the subject's vital capacity. This allowed continuous analysis of the mixed expired gas for F_EO₂ and F_ECO₂ (Marquette mass spectrometer or Applied Electrochemistry S-3A O₂ analyzer and Beckman LB-2 infra-red CO₂ analyzer). Thus, O₂ consumption and CO₂ production (O₂ and CO₂ respectively) were calculated using the nitrogen balance technique during the last 10 sec of each workload.

At peak exercise, peak ventilation – both in absolute terms and as a percentage of the ventilatory reserve – was assessed from forced expired volume in 1 sec. Specifically, the ventilatory reserve was calculated as VE-peak / maximal voluntary ventilation x 100. Maximal voluntary ventilation (MVV) was calculated as [MVV = 27.7 · (FEV₁) + 8.8 · (Predicted FEV₁)].²⁴ Ventilatory pattern at peak exercise was also assessed by the respiratory rate and tidal volume in both absolute terms and as a percentage of forced vital capacity (FVC), and the physiologic deadspace to tidal volume ratio (V_D/V_T), calculated using the Enghoff modification of the Bohr equation, corrected for apparatus dead space²⁵, using end-tidal PCO₂ to estimate arterial PCO₂.²⁶

Analysis

The two groups were compared by unpaired *t*-tests for continuous variables that were normally distributed. A Kolmogorov-Smirnov test was used to assess normal distribution. When variables were not normally distributed, the Mann-Whitney U test was used to compare groups. The relationship between FEV₁ % predicted and age and body mass percentile, and peak power output (W_{peak} % predicted), VO_{2peak} (% predicted) and body mass percentile, and FEV₁ % predicted were evaluated by Pearson correlation coefficients. Paired *t*-tests were used to compare the measured VO_{2peak}, W_{peak}, FVC and FEV₁ with the predicted values that were normally distributed. A Kolmogorov-Smirnov test was used to assess normal distribution. When these variables were not normally distributed, the Wilcoxon-signed rank test

TABLE 1. Anthropometric and spirometry data for bronchopulmonary dysplasia (BPD) and cystic fibrosis (CF) patients.

	BPD patients (mean±SD)	CF patients (mean±SD)
Number of Patients	9	9
Age (yr)	10.0±1.8	9.8±2.0
Height (cm)	135±14	135±13
Weight (kg)	30.9±10.0	29.9±7.2
Body mass percentile (%)	98±11	97±13
FEV ₁ (L)	1.33±0.41	1.54±0.48
FEV ₁ %pred (%)	73±13**	74±14**
FVC (L)	1.88±0.58	1.90±0.58
FVC %pred (%)	86±11**	86±14**

No significant difference between groups for any parameter.

** Differences between measured value and predicted value within group, $P < 0.05$

(Paired- Wilcoxon test) was used to compare groups. A stepwise linear regression was used to assess the effects of nutritional status, lung function, and disease group (cystic fibrosis or bronchopulmonary dysplasia) on exercise capacity. A $P \leq 0.05$ was considered as statistically significant.

Results

The characteristics of the two groups of patients with mild disease are displayed in Table 1.

There were no differences between the two groups for age, anthropometric data, or spirometry. The variables were normally distributed. Within each group the FVC and FEV₁ were lower than the normative predicted value. The FEV₁ % predicted was positively correlated with body mass percentile for cystic fibrosis patients ($r=0.70$, $P<0.05$). In contrast, there was no relationship between FEV₁ % predicted and body mass percentile for bronchopulmonary dysplasia patients.

Mean predicted peak power output for both groups was in the low normal range, with wide variation. Mean predicted peak power output within each group was lower than the measured peak power output ($P < 0.05$). The maximal minute ventilation, the respiratory rate, the tidal volume, or the V_D/V_T ratio showed no difference between the groups (Table 2). However, there was a difference in the respiratory reserve between groups

TABLE 2. Exercise data for bronchopulmonary dysplasia (BPD) and cystic fibrosis (CF) patients.

n = 9 in each group	BPD Patients (Mean±SD)	CF Patients (Mean±SD)
VO ₂ peak (L/min)	1.17 ± 0.32	1.11 ± 0.19
VO ₂ peak (ml/kg/min)	38.6 ± 5.8	38.4 ± 7.2
VO ₂ peak (% pred)	99 ± 16	96 ± 27
HRpeak	186 ± 9	184 ± 10
HRpeak (% pred)	89 ± 5**	88 ± 5**
O ₂ pulse peak (ml/beat)	6.3 ± 1.6	6.0 ± 0.9
O ₂ pulse peak (% pred)	85 ± 42**	82 ± 44**
Wpeak (W)	73 ± 28	67 ± 19
Wpeak (%pred)	88 ± 15**	83 ± 28**
VEpeak (L/min)	44.5 ± 13.4	37.8 ± 9.0
Predicted MVV (L/min)	51.6 ± 15.5	59.2 ± 17.9
VEpeak / predicted MVV, (%)	86 ± 13*	64 ± 26
Respiratory Rate (breaths/min)	63 ± 12	52±17
Tidal Volume (ml)	736±277	782±228
Tidal Volume (% FVC)	39±6	42±5
V _D /V _T (%)	23.2±4.3	21.2±6.6

$p > 0.10$ between groups for all parameters except for VEpeak / predicted MVV, (%)

*Significant difference between groups for VEpeak / predicted MVV, (%), $p < 0.05$

** Significant difference between the measured value and predicted value within group, $p < 0.05$

($P = 0.04$), showing that, unlike cystic fibrosis patients, those with bronchopulmonary dysplasia had a minute ventilation that nearly approached their MVV at peak exercise. The mean peak power output or peak oxygen uptake expressed as a percent predicted or as an absolute value was not different between groups. The mean percent predicted peak oxygen uptake within each group was not different from the measured peak oxygen uptake. Only one subject (CF, male) was below the 95th confidence interval for predicted peak oxygen uptake (55thile).²² This subject's low peak oxygen uptake was likely due to poor effort. There was a good relationship between peak power output and peak oxygen uptake for both groups combined as 83% of the variance in peak power output was explained by peak oxygen uptake (L/min) ($P < 0.05$). When the groups of cystic fibrosis and bronchopulmonary dysplasia patients were combined, there were weak correlations between Wpeak % predicted and body mass percentile ($r=0.47$, $P=0.05$, figure

FIGURE 1. Wpeak % predicted vs Body mass percentile with open circles representing the cystic fibrosis group and the solid black filled circles representing the bronchopulmonary dysplasia group. Regression equation includes both groups combined. $W_{peak} = -0.19 + 0.88 \cdot (\text{body mass percentile})$, $r^2=0.23$, $P < 0.05$, $SEE=19.7\%$, $F\text{-Ratio}=4.7$, statistical power with alpha at 0.05 = 0.52. The 95% prediction intervals (95% confidence intervals for the population) are indicated by the dashed lines.

FIGURE 2. Wpeak % predicted vs FEV₁ %predicted with open circles representing the cystic fibrosis group and the solid black filled circles representing the bronchopulmonary dysplasia group. Regression equation includes both groups combined. $W_{peak} = 30.8 + 0.74 \cdot (\text{FEV}_1 \% \text{predicted})$, $r^2=0.20$, $P=0.06$, $SEE=20.0\%$, $F\text{-Ratio}=3.9$, statistical power with alpha at 0.05 = 0.46. The 95% prediction intervals (95% confidence intervals for the population) are indicated by the dashed lines.

1), and FEV₁ % predicted ($r=0.45$, $P=0.06$, figure 2). Combining these two factors provided a weak correlation ($r=0.56$, $P=0.06$). Adding a grouping factor (0= bronchopulmonary dysplasia, 1= cystic fibrosis) did not improve any of these correlations.

Discussion

This is one of few studies that specifically compares exercise capacities in children with bronchopulmonary dysplasia and cystic fibrosis matched for age, sex, height and FEV₁. In this group of 18 children, we found that both cystic fibrosis and bronchopulmonary dysplasia patients have similar exercise capacities but different ventilatory reserves. Thus, although airflow limitation was the same, the pathophysiology leading to it appears to affect the ventilatory response to exercise. We also demonstrated that both groups experienced a similar cardiac limitation to exercise as peak heart rate and peak oxygen pulse was lower than predicted, resulting in a lower than predicted peak power output.

Bronchopulmonary dysplasia: Like the present study, other work has demonstrated that those with bronchopulmonary dysplasia have increased use of ventilatory reserve during peak exercise compared with matched controls.¹⁵ Their data showed a negative relationship between FEV₁ and peak power output, as we did. One study did show a normal ventilatory reserve of 76% in children with bronchopulmonary dysplasia, which was not different from matched controls, but the reduction in %predicted FEV₁ in those with bronchopulmonary dysplasia was minor (83% predicted) compared with the patients presently described.¹⁸ However, there are other studies that have not reported the ventilatory reserve at peak exercise in children with bronchopulmonary dysplasia.^{16,19} In those studies, the breathing frequency at peak exercise was similar to the present study with the same percent predicted FEV₁ (~71%). Regardless of this fact, peak oxygen uptake in those with bronchopulmonary dysplasia is normal or near normal compared to cycle ergometry predicted values.^{15,16,18}

Cystic Fibrosis: There is more data in the literature on exercise responses in children with cystic fibrosis than in children with bronchopulmonary dysplasia. These studies showed varied peak oxygen uptakes in children with CF in relation to percent predicted values. Similar to this study, other research has demonstrated that the measured peak oxygen uptake in CF children can be close to 100% of predicted when the percent reduced FEV₁ 70 to 81%²⁷. Some studies, unlike the present one, have shown reduced exercise capacity in children with cystic fibrosis with FEV₁'s in the mild to moderate (50-80%) range. A discriminating factor in this range may be FVC; those patients with FVC>80% have a near normal exercise capacity²⁷ whilst those with a lower FVC have a lower exercise capacity.^{6,28} The lower than normal peak power output found in children with moderate cystic fibrosis (FEV₁ = 56% predicted) suggests a component of decreased muscular ability.^{28,29} While the rate of decline in peak oxygen uptake and percent predicted FEV₁ over time in children with cystic fibrosis is 2 ml/kg/min and 3% per year, respectively²⁷, exercise training can reduce the decline by improving peak power output and aerobic capacity in these children.³⁰ Additionally, increased daily physical activity is associated with slower rates of decline in FEV₁³¹ and result in a maintenance of VO₂peak.³² Therefore, exercise training can be promising in children with either condition.

Regardless of the pathophysiology leading to pulmonary impairment, both groups of patients had similar predicted peak power outputs compared to predictive normal values. The peak power output in terms of percent predicted was only weakly predicted by either nutritional status when expressed as body mass percentile, or lung function as predicted by the FEV₁ % predicted. A possible explanation of the minimal effect of nutritional status may reflect the generally good nutritional condition of our patients (body mass percentile: 97 ±12 % for the combined cystic fibrosis and bronchopulmonary dysplasia patients, with only one patient less than 80%), and any possible confounding effect was minimized by the small sample size. Similarly, the

weak correlation between exercise capacity and lung function may relate to the relatively mild pulmonary impairment (only two subjects had a FEV₁ less than 60% predicted). Previous work in cystic fibrosis suggests that exercise in children with cystic fibrosis is impaired significantly only with severe airflow limitation.³³

The relatively narrow range of pulmonary function and nutritional status in both the cystic fibrosis and bronchopulmonary dysplasia patients limits some of the predictive ability of the study. Still, significant trends relating exercise capacity to both lung function and nutritional status are consistent with previous reports.

Although the lack of a healthy control group is a limitation of this study, use of normative historical control data allows percent predicted values to be constructed. By using a percent predicted value, we control for age, height and sex. These results support the concept that the etiology of the pulmonary impairment is not the most important determinant of the exercise capacity of the patients. The pulmonary abnormality results from different mechanisms of injury - progressive chronic inflammatory changes for cystic fibrosis in contrast to barotrauma and oxygen toxicity for bronchopulmonary dysplasia, different timing of the parenchymal insult, and postnatal progressive summation of ongoing chronic infection for cystic fibrosis in contrast to a limited perinatal injury with subsequent growth and repair for bronchopulmonary dysplasia. These subjects were matched for the severity of lung injury at the time of evaluation with the result that the work capacity was not different between groups, although slightly but significantly lower than predicted values. This suggests that the severity, rather than the etiology of the disease process, is the determining factor. Longitudinal studies in both populations and work on an older group of survivors for each condition would be of great interest.

In conclusion, while our patients with mild bronchopulmonary dysplasia and mild cystic fibrosis arrived at similar lung function characteristics as assessed

by spirometry through different pathological mechanisms, they had similar aerobic capacities. Both groups experienced a similar cardiac limitation evidenced by their lower than predicted heart rate and oxygen pulse at peak exercise which resulted in lower than predicted power output at peak exercise. The greater use of respiratory reserve in the bronchopulmonary dysplasia group suggests that they may be at higher risk for problems of pulmonary gas exchange, and this may become more evident as these patients age.

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Correspondence to:

G.S. Zavorsky PhD
 Saint Louis University School of Medicine
 Obstetrics, Gynecology & Women's Health
 6430 Clayton Road, Suite 290
 Saint Louis, MO 63117
 Phone number: (314) 977-2574
 Fax number: (314) 977-2161
 zavorsky@slu.edu