Exercise-induced alveolar hypoventilation in long-term survivors of bronchopulmonary dysplasia

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Summary

Background We aimed to confirm that children who have survived bronchopulmonary dysplasia (BPD) display lower ventilation during exercise than healthy children, and to determine whether alveolar hypoventilation associated with exercise-induced hypoxemia occurred in these children.

Methods Twenty children with BPD (birth weight 1441±523 g [mean ± SD], gestational age 31±2.3 weeks), aged 7 to 14 years, and 18 matched healthy children, born at term, performed resting pulmonary function and cardiopulmonary incremental exercise tests. Arterialized capillary blood gases were measured at rest and at maximal exercise in the BPD group.

Results The BPD group showed moderate expiratory airflow limitation and hyperinflation. Maximal oxygen uptake and ventilatory threshold were similar in the two groups. The BPD group displayed ventilatory limitation on exercise, with greater use of the ventilatory reserve (p<0.01), and lower maximal ventilation (p<0.01), and tidal volume (p=0.01). Changes in ventilation (p<0.0001) and tidal volume (p=0.003) during exercise were significantly smaller in the BPD group than in controls, at similar submaximal workloads. At peak exercise, we observed hypoxemia in 12 BPD children (60%). In the subgroup with hypoxemia, a significant increase in PaCO₂ (p=0.01) was measured at peak exercise, showing alveolar hypoventilation sustained by the lower tidal volume.

Conclusions Despite normal maximal aerobic performance, BPD children showed ventilatory limitation on exercise, frequently with hypoxemia and alveolar hypoventilation. Despite an improvement in their pulmonary condition, continued follow-up by cardiopulmonary exercise testing, is strongly recommended.

Key words: Bronchopulmonary Dysplasia • Hypoxemia • Alveolar Hypoventilation • Exercise • Children
The prevalence of bronchopulmonary dysplasia (BPD) has failed to decline despite advances in antenatal management and neonatal intensive care [1]. With advancing age, the lung abnormalities improve, and most patients are free of symptoms by the time they start school. Lung function monitoring is required to detect clinically silent residual abnormalities, which may cause symptoms in adulthood [2-5]. The severity of these abnormalities (i.e., bronchial obstruction, bronchial hyperreactivity, and alveolar distension) correlates with gestational age at birth and the duration of neonatal oxygen therapy [2-7].

In several studies of children with a history of BPD, exercise tolerance was assessed based on maximal oxygen capacity (VO_{2\text{max}}). The results were conflicting, with no difference versus controls in some studies [6-8] and a decrease in VO_{2\text{max}} in others [9-10]. These discrepancies may be related to differences across study populations regarding birth weight and gestational age at birth. A review article established that greater severity of lung-function-test abnormalities was associated with greater severity of exercise intolerance [11].

Independently from the level of exercise tolerance, many patients have abnormal ventilatory responses to exercise (e.g., exhaustion of the ventilatory reserve and low ventilatory flow rates at submaximal exercise levels) and a few exhibit hypoexaemia while exercising [6-7, 9-13]. Hypotheses put forward to explain the development of hypoexaemia during exercise include a ventilation/perfusion (V/Q) mismatch [7] and a decrease in the alveolar surface area [13]. Alveolar hypoventilation may be involved, given that BPD patients seem unable to increase their minute ventilation (VE) to meet the metabolic demands of exercise [9]. Further support for alveolar hypoventilation comes from a study showing higher transcutaneous PCO2 values during exercise in BPD children than in controls [6]. In another study, however, the end-tidal CO2 pressure (PETCO2) used as a measure of alveolar hypoventilation was not different between BPD patients and controls [7]. However, there is some doubt about the accuracy of PETCO2 measurements, most notably in patients with lung diseases involving V/Q mismatching. The definitive diagnosis of alveolar hypoventilation requires blood gas measurements to detect hypercapnia. Here, our objective was to investigate whether exercise-induced hypoexaemia in long-term BPD survivors was associated with hypercapnia, as assessed by blood gas measurement.

**Methods**

**Population**

In 2000-2001, we prospectively studied 20 patients (7 girls and 13 boys) aged 7 to 14 years who had survived BPD defined as oxygen dependence for at least 28 days from birth [14]. On the study day, 4 patients were on long-term bronchodilator therapy (salmeterol, n=3; or formoterol, n=1) and 15 were on inhaled corticosteroid therapy. None of the patients had experienced acute respiratory symptoms within the last 6 weeks, and the physical examination was normal on the study day.

The controls were 18 children (10 girls and 8 boys) aged 7 to 14 years who were referred for exercise testing as part of screening prior to sports participation. All 18 children were born at full term, and none experienced respiratory or other abnormalities during the neonatal period. Except for 2 girls in each group, all BPD patients and controls were prepubertal. Informed consent was obtained from the parents of all patients and controls.

**Lung function testing at rest**

Conventional spirometry was performed as recommended by the European Respiratory Society [15] in both the BPD patients and the controls. The helium dilution technique was used to measure forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and functional residual capacity (FRC). To measure the diffusing capacity of the lung for carbon monoxide (DLCO), we used the single-breath method with correction for alveolar volume (VA) [16]. Lung function parameters were expressed as the percentage of the predicted values for age and sex [17]. FRC and the ratio of FRC over total lung capacity (TLC) served to assess alveolar distension.

**Exercise testing**

Exercise testing was performed on either a bicycle ergometer with electromagnetic braking (Lode BV, Groningen, The Netherlands) or a motor-driven treadmill (Marquette Electronics, Milwaukee WI, USA) depending on the size of the child. Breath-by-breath gas exchange measurements were obtained using the Vmax 29c system (SensorMedics, Yorba Linda, CA, USA). The child breathed through a pneumotachograph (dual hot-filament flow sensor) with a dead space of only 15 mL. The gas samples were conveyed through a Perma Pure capillary (using the osmosis technique) to a non-dispersive infrared CO2 analyser and to a differential-pressure paramagnetic O2 analyser. Continuous monitoring of the electrocardiogram (Marquette Max-I, Milwaukee, WI, USA) and pulse oxygen saturation (SpO2; Ohmeda 3700, Louisville, KY, USA) was performed.

In the BPD patients, PO2 and PCO2 were determined in arterioised capillary blood sampled at the earlobe [18-19]. Arterialisation of earlobe capillary blood was achieved via the topical application of a irritant (Finalgon®, Boehringer Ingelheim, Barcelona, Spain) for 5 minutes in order to increase the arteriovenous PO2 difference. The blood samples were examined immediately using an analyser located in the exercise-testing room (AVL OPTI analyser, AVL Instruments Médicaux, Cergy Pontoise, France).

In each child, a standardised questionnaire [20] was used to estimate the weekly level of physical activity, which was expressed as metabolic equivalents (MET).

**Protocol**

The study measurements were performed at the lung function laboratory of the paediatric pulmonology department, Necker Enfants-Malades Teaching Hospital, Paris,
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France. The same protocol was used in all study participants. At rest, an electrocardiogram was recorded and spirometry was performed. Maximal voluntary ventilation (MVV) was computed as FEV\textsubscript{1}/35 [21]. Then, the exercise test was explained to the child.

A triangular exercise test protocol with an incremental workload was used. The workload increase was adapted to each individual [22]. Briefly, the total duration of the test was 10 to 12 minutes. A rest period during which the child was observed for 3 to 5 minutes was followed by a 3-minute warm-up period with a workload equal to 20% of the predicted peak workload (W\textsubscript{max}). Then, during an 8-minute exercise period, 10% of W\textsubscript{max} was added every minute. The ECG and SpO\textsubscript{2} were monitored continuously throughout the test. Maximal exercise was considered achieved when at least two of the following three criteria were met: clinical exhaustion or inability to maintain the required pedalling speed (60 rpm) or treadmill speed despite strong verbal encouragement, a VO\textsubscript{2} plateau despite the increasing workload, and a heart rate at least equal to the predicted maximum heart rate (HR\textsubscript{max} = 210 - (0.65 × age) ±10%).

Values for the following variables obtained during exercise testing were averaged over 10-s periods: VO\textsubscript{2}, VE, ventilation pattern variables (breathing rate [BR], tidal volume [VT], mean inspiratory flow [VT/inspiratory time, VT/Ti], and inspiratory time over total breath duration [Ti/Tot]), and estimated physiologic ratio of dead-space over VT (VD/VT). Peak values were measured at W\textsubscript{max} and submaximal values were measured during the warm-up period and subsequent workload increments. The ventilatory threshold (V\textsubscript{Th}) was determined automatically by the exercise-test software and was checked by one of the investigators based on the VO\textsubscript{2}-V\textsubscript{CO}\textsubscript{2} relationship [23].

Samples for blood gas measurements were collected at rest (while the child breathed through the pneumotachograph) and at peak exercise. Hypoxaemia was defined as an at least 5% PaO\textsubscript{2} decrease at peak exercise compared to rest [21]. The alveolo-arterial oxygen gradient (P(A-a)O\textsubscript{2}) was computed as the difference between PaO\textsubscript{2} and alveolar O\textsubscript{2} tension (PAO\textsubscript{2}) obtained as follows: PAO\textsubscript{2}=150-PaCO\textsubscript{2}/R (where R is the respiratory quotient and PaCO\textsubscript{2} the partial pressure of CO\textsubscript{2} in arterial blood).

Hypoxaemia was defined as an at least 4% absolute SpO\textsubscript{2} decrease compared to the highest value obtained at rest [21].

Statistics

Descriptive statistics are reported as mean±SD. We used the Mann-Whitney test for between-group comparisons of anthropometric and spirometric variables, VO\textsubscript{2 max}, and ventilation pattern variables. The Wilcoxon test for paired samples was used to compare blood gas values at rest and at peak exercise intensity in the BPD group. Correlations between quantitative variables were assessed based on Spearman’s rank correlation coefficient.

All variables were log-transformed because their distributions were highly skewed. Changes in variables with exercise were assessed as follows: exercise variables were calculated at rest and at four submaximal and maximal workloads, corresponding to 40, 60, 80, and 100% of the measured VO\textsubscript{2 max} for each child. We then compared changes in these exercise variables over time in the two groups using generalized estimating equation (GEE) analysis, with a robust estimation of the variance [24]. GEE analysis can be used to determine population-averaged estimates, accounting for correlations between repeated observations. Classical ANOVA is not appropriate for this purpose. With GEE analysis, correlations linking repeated measures over time are taken into account. An interaction term for group by time was included in the model to evaluate differences in the variation of each variable during exercise. Then the interaction term was excluded from the model if it was not significantly different from 0.

All statistical analyses were done using SAS software (SAS Institute, Cary, NC) including the GENMOD procedure [25]. Values of p smaller than 5% were considered statistically significant.

Results

Population

In the BPD group, birth weight was 1441±523 g, gestational age was 31±2.3 weeks, mechanical ventilation duration was 145.1±130.1 days (not counting nocturnal home ventilation, which was used by 7 children for 21.1±9.3 months), and oxygen therapy duration was 25.3±30.2 months (including home oxygen therapy).

The anthropometric characteristics at the time of the study are reported in Table I. None of the children reported being limited in their everyday activities. In the BPD group, 5 patients had a history of upper respiratory tract infection, coughing episodes, and episodes of non-wheezing bronchitis during the first postnatal year.

Lung function at rest

In the BPD group, the values obtained at rest indicated bronchial obstruction and alveolar distension (Table I). No differences were found between the two groups for DL\textsubscript{CO} or DL\textsubscript{CO}/VA. FEV\textsubscript{1} was not measured at exercise completion. A single child experienced clinical bronchospasm (cough requiring two puffs of a bronchodilator).

Mechanical ventilation duration during the neonatal period was significantly correlated with FEV\textsubscript{1} at rest (p=0.003, r\textsuperscript{2}=0.42) (fig. I). No significant correlations were found between lung function parameters at rest and the duration of neonatal oxygen therapy, gestational age at birth, or birth weight.

Exercise test results

Exercise tolerance

Of the 20 BPD patients, 12 exercised on a treadmill and 8 on a bicycle ergometer. Corresponding numbers in the
The proportion of ventilatory reserve (VE \(_{max}/MVV\)) and had lower peak values of VT, VE, Ti/Ttot, and VT/Ti.

The exercise-induced increases in VE, VT, VTi, and Ti/Ttot were significantly smaller in the BPD group than in the control group at all four exercise intensities tested (GEE, \(p<0.0001, p=0.003, p=0.01,\) and \(p=0.003,\) respectively) (fig. 2).

The lower VE values were due to lower VT values during exercise. At each exercise intensity, BR was not different between the two groups. Neither were differences in exercise-induced VD/VT changes found between the two groups.

### Blood gas values in arterialised capillary blood

Oxygen saturation was estimated by pulse oximetry (SpO\(_2\)) in both groups. In the BPD group, mean SpO\(_2\) was 97.7\(\pm\)1.2\% at rest and 93.1\%\(\pm\)3.4\% at peak exercise (\(p<0.001\)). In the control group, mean SpO\(_2\) was 98\%\(\pm\)0.97\% at rest and 97\%\(\pm\)1.03\% at peak exercise. The SpO\(_2\) difference between rest and peak exercise was 4.5\%\(\pm\)3.3\% in the BPD group and 0.88\%\(\pm\)1.26\% in the control group (\(p<0.001\)).

Blood was drawn for blood gas measurements in the BPD group only. Mean capillary blood gas levels were available for 16 of these 20 patients (Table II), including 9 of the 12 patients who exhibited exercise-induced oxygen desaturation. In all 9 patients, exercise was associated with significant PaCO\(_2\) elevation (Table III).

The subset of BPD patients with exercise-induced desaturation included all 4 patients on long-acting bronchodilator therapy. The patient who experienced bronchospasm was not on preventive beta2-agonist therapy and had hypoxaemia at peak exercise.

The duration of neonatal mechanical ventilation correlated significantly with PaCO\(_2\) (\(r^2=0.33\)) but not with PaO\(_2\). None of the blood gas values correlated significantly with the duration of neonatal oxygen therapy or gestational age at birth. FEV\(_1\) correlated positively with PaCO\(_2\) (\(r^2=0.25, p=0.04\)) and negatively with PaO\(_2\) (\(r^2=0.31, p=0.02\)) (Fig. 1).

### Discussion

We studied the responses to exercise in 20 BPD survivors with a mean age of 10 years, all of whom had airway obstruction. They were able to maintain an aerobic capacity similar to that in the control group, at the expense of ventilatory limitation (use of the ventilatory reserve and lower HR\(_{max}\)). In 12 of the 20 BPD children, oxygen desaturation developed during exercise testing. Blood gas measurements were available for 9 of these 12 patients and consistently showed hypercapnia at maximal exercise, indicating alveolar hypoventilation (Table IV).

Exercise-induced hypoxaemia is well known to occur in children with a history of BPD [7, 9-10, 12]. Nevertheless, the proportion of patients with exercise-induced desaturation was high in our study. Our patients had the classic form of BPD, and their gestational age at birth (29-31 weeks) and birth weight (>1200 g) indicated impairment of the sacculary stage of lung development. Only 6 patients received surfactant as part of their neonatal management. The patients had long periods of exposure to barotrauma and oxygen toxicity. Thus, comparatively to the above-referenced studies, they had longer durations of mechanical ventilation; and their
times on oxygen therapy were longer than in all but one of the previous studies [7]. It would be of interest to investigate whether advances in neonatal management have decreased the proportion of patients with hypoxaemia. We found correlations linking FEV₁ to both PaO₂ at peak exercise and mechanical ventilation duration, which support an association between greater severity of bronchial obstruction/BPD and the exercise-induced blood gas abnormalities [11].

One possible limitation of our study is the use of arterialised capillary blood for the blood gas measurements. Recent studies in adults challenge the validity of PO₂ measurements in arterialised capillary blood when values exceed 80 mm Hg [26-28]. In children, however, no systematic PO₂ difference between arterial and capillary blood has been found [18]. In adults with chronic obstructive pulmonary disease, hypoxaemia during maximal exercise was more pronounced with a treadmill than a bicycle ergometer [29]. Of our 12 patients with exercise-induced hypoxaemia, 7 (58.3%) used a treadmill, compared to 5 (62.5%) of the 8 patients without exercise-induced hypoxaemia. These proportions do not support a role for preferential treadmill use in the high proportion of patients with exercise-induced hypoxaemia.

Table II.
Aerobic capacity and ventilation pattern at peak exercise. The values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>BPD n=20</th>
<th>Controls n=18</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max (ml/kg/min)</td>
<td>43.8 (8)</td>
<td>43.1 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>VTh (ml O₂/kg/min)</td>
<td>29.0 (6.8)</td>
<td>26.5 (6.6)</td>
<td>NS</td>
</tr>
<tr>
<td>HRmax (bpm)</td>
<td>185.6 (11.6)</td>
<td>197.2 (10.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SpO₂max (ml/beat)</td>
<td>6.4 (2.0)</td>
<td>6.9 (2.5)</td>
<td>NS</td>
</tr>
<tr>
<td>VEmax (L/min)</td>
<td>40.6 (12.2)</td>
<td>53.2 (15.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VE₅₀/MVV (%)</td>
<td>91.8 (19.9)</td>
<td>80.1 (14.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VT₅₀ (L)</td>
<td>0.63 (0.20)</td>
<td>0.81 (0.24)</td>
<td>0.01</td>
</tr>
<tr>
<td>VTmax/FVC (%)</td>
<td>36 (11)</td>
<td>38 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>BR₅₀ (breaths/min)</td>
<td>61.7 (10.0)</td>
<td>64.6 (8.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Ti₅₀/Ttot₅₀ (%)</td>
<td>46.4 (3.6)</td>
<td>50.2 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VT/Tmax (L/s)</td>
<td>1.32 (0.45)</td>
<td>1.75 (0.58)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

BPD, bronchopulmonary dysplasia; VO₂max, maximal oxygen capacity; VTh, ventilatory threshold; HRmax, maximum heart rate; SpO₂max, maximum oxygen saturation by pulse oximetry; VE₅₀, maximum minute ventilation; MVV, maximum voluntary ventilation; VT₅₀, maximum tidal volume; FVC, forced vital capacity; BR₅₀, maximum breathing rate; Ti₅₀, maximum inspiratory time; Ttot₅₀, maximum total breathing cycle time.
Exercise is normally associated with an increase in P(A-a)O₂ that reflects V/Q mismatching and oxygen diffusion limitation. In BPD children, V/Q mismatching may increase with exercise. In our study, however, only 2 BPD patients had P(A-a)O₂ values greater than 35 mm Hg, and the exercise-induced VD/VT changes were similar in the BPD and control groups, suggesting that no major changes in V/Q matching occurred with exercise [30]. Other hypotheses put forward to explain exercise-induced hypoxaemia in BPD children include exercise-induced bronchospasm [10] and decreased oxygen diffusion [13], neither of which can be excluded based on our data.

Hypoxaemia is the rule in individuals with alveolar hypoventilation. Exercise increases ventilation and therefore decreases PaCO₂ [31-32]. In our study, mean PaCO₂ was not lower at peak exercise than at rest in the overall BPD population (Table III) or in the subgroup with exercise-induced hypoxaemia (Table IV). We found statistically significant PaCO₂ increases with exercise in 9 of the 12 BPD children who exhibited exercise-induced hypoxaemia. Thus, these 9 patients met the definition of alveolar hypoventilation [33] at peak exercise. Another study obtained similar findings, with increasing tcPCO₂ values as the hypoxaemia worsened [6]. However, there were only 4 BPD children and tcPCO₂ is only an indirect measure of PaCO₂ during exercise. In contrast to PO₂, PCO₂ and pH values measured on arterialized capillary blood are known to be valid [26-28].

Alveolar hypoventilation during exercise in BDP patients is associated with failure to increase VT [6, 9]. Several explanations can be put forward. In BPD patients, bronchial obstruction under basal conditions may lead to a decrease in PaO₂ and to an increase in PaCO₂. This possibility is supported by the correlations found in our study between FEV₁ and both PaO₂ and PaCO₂. Exercise-induced PaCO₂ elevation is associated with a decrease in Ti/Ttot, which coincides with the VT decrease. As a result, VT/Ti fails to increase during exercise and VT therefore declines. Similar results were obtained in children with cystic fibrosis.

**Table III.**
Blood gas values in 16 patients with a history of bronchopulmonary dysplasia. The values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak exercise</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>95.7 (10.7)</td>
<td>85.4 (9.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>36.4 (3.6)</td>
<td>38.6 (4.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (0.03)</td>
<td>7.34 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P(A-a)O₂ (mm Hg)</td>
<td>12.3 (10.6)</td>
<td>272 (10.0)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

PaO₂, partial pressure of oxygen in arterialized capillary blood; PaCO₂, partial pressure of carbon dioxide in arterialized capillary blood; P(A-a)O₂, alveolar-to-arterial oxygen difference.

**Table IV.**
Blood gas values in 9 of the 12 bronchopulmonary dysplasia survivors who had exercise-induced oxygen desaturation. The values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak exercise</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>93 (6.32)</td>
<td>79.1 (6.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>373 (3.7)</td>
<td>411 (3.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 (0.03)</td>
<td>7.34 (0.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>P(A-a)O₂ (mmHg)</td>
<td>14.0 (13.8)</td>
<td>31.7 (9.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PaO₂, partial pressure of oxygen in arterialized capillary blood; PaCO₂, partial pressure of carbon dioxide in arterialized capillary blood; P(A-a)O₂, alveolar-to-arterial oxygen difference.
sensitivity to CO2. Studies in preterm babies with BPD showed degree of chronic bronchial obstruction and the inherent sen-
itive pulmonary disease may be a feature in BPD patients, as suggested by the alveolar distension at rest and low VT values during exercise. Dynamic hyperinflation leads to CO2 retention during exercise [35-36]. Inspiratory capacity and flow-volume curves during exercise, which were not investigated in our study, should be performed in future studies to confirm the existence of dynamic hyperinflation [38].

Another explanation to the alterations in blood gas exchange and inadequate CO2 clearance is an increase in inspiratory muscle workload [39]. Increased inspiratory workload, in combination with shallow breathing, impairs CO2 clearance, and low VT inevitably leads to increased dead-space ventilation and therefore to alveolar hypoventilation with PaCO2 elevation. Alveolar distension and bronchial obstruction at rest result in a higher inspiratory muscle workload during exercise. One strategy for avoiding excessive muscle fatigue may consist in tolerating some degree of PaCO2 elevation, as suggested previously for children with cystic fibrosis [39].

When ventilatory flow is under the control of CO2, minute ventilation is the result of a compromise between the degree of chronic bronchial obstruction and the inherent sensitivity to CO2. Studies in preterm babies with BPD showed blunted central inspiratory responses and delayed postnatal resetting of the carotid chemoreceptors [40]. Repeated hypoxic episodes in infancy may compromise the acquisition of normal chemoreceptor sensitivity. Measuring the mouth occlusion pressure (P0.1) during exercise may prove helpful. P0.1 is the pressure generated at the mouth during the first 100 ms of an inspiratory effort performed with the airways occluded. P0.1 evaluates the activity of the inspiratory centres independently from respiratory system compliance or the degree of bronchial obstruction. The demonstration that P0.1 increases during exercise would consist evidence that the central respiratory drive is normal [41].

In our study, the blood gas alterations in the BPD patients did not seem to adversely impact exercise capacity, as VO2max values were similar to those in the control group. A methodological bias related to the use of two different exercise devices cannot be completely ruled out. Evaluating exercise tolerance is crucial in children with chronic respiratory diseases, as it cannot be easily predicted from basal respiratory function [7,9]. In keeping with earlier studies [4, 6-8, 12], we found that aerobic capacity (VO2max, AT) was similar in the BPD patients and the controls. Only two studies found lower VO2 values during submaximal exercise in BPD patients than in controls [9] [10]. However, the exercise intensities may have been different in the two populations: although the comparisons were done at the same exercise time points [9] or at the same submaximal power outputs [10], total exercise duration was significantly shorter in the BPD group, indicating that the levels of exercise at which measurements were made did not reflect similar exercise intensities in the BPD patients and controls [9-10]. In our study, VO2 during submaximal exercise was measured at the same exercise intensities in the two groups and expressed as the percentage of VO2max in each child. By individually tailoring the workload increments, we were able to determine VO2max in each child [22]. These methodological differences probably explain the VO2max discrepancies across studies of BPD children. VO2max in our study correlated neither with birth weight nor with the durations of mechanical ventilation or oxygen therapy in the neonatal period, in keeping with earlier studies showing no relationship between the severity of the neonatal disease and VO2max [6-7, 9, 11].

In conclusion, cardiopulmonary exercise testing is useful for detecting respiratory function impairments in BPD survivors. We advocate repeated exercise testing as part of the regular follow-up of these patients, starting as soon as age permits, with SpO2 determinations and, if needed, blood gas measurements. Such testing can achieve the important goal of detecting blood gas exchange alterations and, thus, assessing the long-term risk of pulmonary arterial hypertension.

It would be of interest to determine whether exercise induces alveolar hypoventilation in the new form of BPD, which occurs at the alveolar stage of lung development, in preterm babies born at younger gestational ages. Furthermore, additional studies should elucidate the mechanisms involved in the exercise-induced alveolar hypoventilation seen in BPD survivors.

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References


