Hyperventilation during Exercise in Very Low Birth Weight School-Age Children may Implicate Inspiratory Muscle Weakness

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Objectives To study the ventilatory response during exercise in 8- to 10-year-old children born in 1998 to 2000 with a birthweight <1500 g (very low birthweight [VLBW]).

Study design We studied 19 VLBW children and 20 full-term children paired for age and sex. A physical activity questionnaire was administered. Lean body mass, spirometry, and maximal inspiratory pressure were assessed at rest. Gas exchange, breathing pattern, and the tension-time index of the inspiratory muscles, a noninvasive indicator of inspiratory muscle effort, were evaluated during a continuous incremental cycling protocol.

Results VLBW children had lower weight, height, lean body mass, and maximal inspiratory pressure than control subjects. Their physical activity level was not different. During exercise, they had a higher respiratory rate and minute ventilation for the same metabolic level (VCO_2/kg) and a higher tension-time index of the inspiratory muscles for the same exercise level (percentage of maximal oxygen consumption).

Conclusions The lower inspiratory muscle strength observed in school-age VLBW children resulted in a higher inspiratory effort during incremental exercise. The rapid but not shallow breathing pattern adopted by this population during exercise may have been in response to their lower inspiratory muscle resistance to fatigue. VLBW children complaining of dyspnea should be investigated with exercise testing. *(J Pediatr 2012;160:415-20)*.

It remains unclear whether the long-term respiratory outcome of very preterm infants has changed with the increased survival rate at lower gestational age and the advances in ventilatory management strategies.[1] Antenatal steroids and surfactant have lowered the mortality rate, especially of more immature children at higher risk for lung injury and long-term respiratory sequelae.[1] However, changes in ventilatory modalities, including the development of noninvasive ventilation techniques and lowered oxygen saturation goals, have modified the short-term respiratory outcomes.[2] To date, the studies assessing the long-term respiratory outcome of very low birthweight (VLBW) children have shown a higher prevalence of airways obstruction and gas trapping[3] and the lower diffusion capacity of the lungs at rest.[4] Exercise performance, evaluated at the end of the first decade with the measurement of maximal oxygen consumption ($VO_{2\ max}$), has been highly variable.[5-9] However, analysis of the physiological systems involved during exercise adaptation has shown normal cardiovascular function,[5,10] but abnormal ventilatory responses.[5-9] These abnormalities were more striking when the children had a history of bronchopulmonary dysplasia (BPD).

The great heterogeneity in the breathing pattern adopted by VLBW children during exercise remains unexplained.[5,7-9] We hypothesized that it may be linked to the variable level of inspiratory muscle effort produced at each breath during exercise. An obstructive syndrome with alveolar hyperinflation may impose an increased load on the inspiratory muscles, which would modify the ventilatory pattern adopted during exercise.[11] The noninvasive tension-time index of the inspiratory muscles ($TT_{0.1}$) has been proposed to assess inspiratory muscle effort during exercise in children with cystic fibrosis.[12] $TT_{0.1}$ integrates all the components that may affect the respiratory muscles during exercise, including breathing cycle timing, inspiratory demand, and maximal inspiratory force reserve. Our goal was to compare the inspiratory function at rest and during exercise in a recent cohort of VLBW children and healthy term-born children paired for age and sex.

Methods

The VLBW group was recruited from a cohort of 79 children, 8 to 10 years old, born between 1998 and 2000 before 29 weeks of gestation with a birthweight <1500 g, and observed longitudinally at Montpellier University Hospital Center. Inclusion criteria

BPD	Bronchopulmonary dysplasia	$P_{i\ max}$	Maximal inspiratory pressure
FRC	Functional residual capacity	$P_{0.1}$	Occlusion pressure
HR	Heart rate	RR	Respiratory rate
LBM	Lean body mass	$TT_{0.1}$	Tension-time index of the inspiratory muscles
MAQ	Modifiable Activity Questionnaire		
MET	Metabolic equivalents of task	VLBW	Very low birthweight
$PetCO_2$	Tidal expiratory pressure of carbon dioxide	$VO_{2\ max}$	Maximal oxygen consumption
		VT	Tidal volume

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were a need for supplemental oxygen ≥28 days for the BPD subgroup[13] and a need for supplemental oxygen ≤10 days for premature infants without BPD (no-BPD). Exclusion criteria were a need for supplemental oxygen for 10 to 27 days, cerebral palsy that precluded exercise testing because of physical or cognitive deficits, relative or absolute contraindication to perform an incremental exercise test referenced by the American Thoracic Society,[14] and use of medications not part of the pharmacological management of BPD and liable to cause exercise limitation (alpha- and beta-blockers, amiodarone, digitalis, and calcium channel blockers).

The control group was recruited through the press and matched for age and sex with the VLBW children. Inclusion criteria were term birth (≥37 weeks of gestation), normal birth weight according to the national reference curves, and no cardiac, pulmonary, or muscular disease or overt physical or mental disability. Exclusion criteria were relative or absolute contraindication to perform an incremental exercise test[14] and intensive training defined as sports practice amounting to >6 hours per week.

We obtained informed written consent from all the children and their two parents. The protocol was approved by the local ethics committee (Comité de Protection des Personnes Sud Méditerranée IV).

Protocol

All participants came to the pulmonary function laboratory at Arnaud de Villeneuve Hospital in Montpellier for a 4-hour assessment. Anthropometric measurements were made and respiratory function was assessed at rest and during a maximal incremental cycling exercise. Physical activity was assessed with a self-administered questionnaire.

Anthropometric Measurements. Weight and height were measured, and the body mass index was calculated as weight in kilograms divided by height in square meters (kg/m^2). Lean body mass (LBM) was assessed with impedance and skinfold measurements. The values given by both methods were averaged to balance the variability of the two methods.

Bicipital, tricipital, subscapular, and suprailiac skinfold thicknesses were measured with a Harpenden skinfold caliper (Eugedia, Cachan, France). Body fat mass was assessed according to the 4-skinfold-thickness measurements of Durnin and Rahaman.[15] LBM was calculated by subtracting body fat mass from total body mass.

Body composition was determined with bioelectrical impedance with a multifrequency impedance analyzer (body impedance analyzer, model BIA 101/S; Akern/RJL Systems, Clinton Township, Michigan) with the following frequencies: 1, 5, 10, 50, and 100 kHz.

Respiratory Function at Rest. Spirometry and lung volumes were performed at rest with a body plethysmograph (Bodybox 5500; Medisoft, Lille, France) by skilled pulmonary function technicians who work regularly with children, following the recommendations of the American Thoracic and European Respiratory Societies.

Maximal inspiratory pressure ($P_{i\ max}$) was measured at rest at functional residual capacity (FRC) on seated subjects, with a Validyne MP45 pressure transducer (Validyne Engineering, Northridge, California) (± 250 cm H_2O), with the technique of Black and Hyatt.[16]

Gas Exchange, Ventilatory Pattern, and $TT_{0.1}$ during Exercise. A maximal incremental exercise test was performed on a cycle ergometer (Ergomeca GP440, La Bayette, France), according to a standardized protocol for children.[17] Inspiratory muscle effort was assessed at each level of exercise with the noninvasive measure of $TT_{0.1}$, as previously described.[12]

Physical Activity Questionnaire. Physical activity and energy expenditure over the past year were assessed with the French version of Kriska's Modifiable Activity Questionnaire (MAQ).[18] The MAQ was administered to both parents and child. They were asked to indicate the activities the child had engaged in at least 10 times during the past year from among a list of common leisure activities. They could also report activities that were not included on the list. An estimate of the energy expenditure in the past year was then calculated and expressed in metabolic equivalents of task (MET).

Statistics

The lung function test results were analyzed as percentages of the reference values.[19] Medians (25th and 75th values) are reported. The Mann-Whitney rank sum test was used for comparisons between VLBW and control groups and between BPD and no-BPD groups. The $\chi 2$ test was used for categorical data. Forward stepwise analysis was applied to assess factors associated with $P_{i\ max}$.

A linear mixed model compared the continuous variables between groups to take in account the multiple observations per patient during the incremental exercise test. All analysis was carried out with the SAS/UNIX statistical software (SAS version 9, SAS Institute, Cary, North Carolina). Statistical significance was defined as a P value <.05 (two-sided).

Results

Perinatal Characteristics of the Study Population

Of the 79 VLBW children who survived to hospital discharge, 51 were eligible: 20 without BPD and 31 with BPD. Thirty-two of these eligible patients were not enrolled: 20 were lost during follow-up, and 12 declined to participate in the study. Nineteen children were thus included in the VLBW: 9 without BPD (no-BPD) and 10 with BPD (BPD). None of the antenatal, neonatal, or postnatal data for known risk factors or markers of BPD differed between the included and non-included children (**Table I**; available at www.jpeds.com).

Their gestational age was 27.0 weeks (range, 26.0-27.0 weeks), and the birthweight was 850 g (range, 730-1000 g). Surfactant treatment was given to 84% of the cases, and 32% received a first course of cyclooxygenase inhibitor for persistent ductus arteriosus. The durations of invasive mechanical ventilation and supplemental oxygen were 5.0 days (range, 1.5-11.5,