Resting energy expenditure in children with neonatal chronic lung disease and obstruction of the airways

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Children with history of broncho-pulmonary dysplasia (BPD) often suffer from growth failure and lung sequelae. The main objective of this study was to test the role of pulmonary obstruction on resting energy expenditure (REE) and nutritional status in BPD. Seventy-one children with BPD (34 boys and 37 girls) and thirty controls (20 boys and 10 girls) aged 4–8 years were enrolled. Body composition was assessed by bio-impedance-metry measurements; REE was measured by indirect calorimetry. Predicted REE was calculated using the Schofield equation. The population of children with BPD was divided into three groups: children without obstruction of the airways, children with moderate obstruction of the airways, and children with severe obstruction. Children with BPD were significantly smaller and leaner than controls. Altered body composition (reduction of fat mass) was observed in BPD children that suffered from airway obstruction. REE was significantly lower in children with BPD compared to controls, but when adjusted for weight and fat-free mass no significant difference was observed irrespective of pulmonary status. Airway obstruction in children with BPD does not appear to be associated with an increased REE. Moreover altered REE could not explain the altered nutritional status that is still observed in BPD in later childhood. This supports the hypothesis that body composition and pulmonary function in BPD in later childhood are fixed sequelae originating from the neonatal period.


Bronchopulmonary dysplasia (BPD) is still a frequent complication in infants born very prematurely1. Factors that are known to influence the metabolic rate in the preterm neonate include illness, activity, composition of food and thermal environment2. Preterm neonates with neither intrauterine growth retardation nor BPD usually show catch-up growth before the age of 2 years. In later childhood, preterm children without BPD have normal nutritional status and normal resting energy expenditure (REE) even if a part of preterm still demonstrated positive metacholine provocation test3. Conversely, children with BPD often suffer from undernutrition and several studies have demonstrated higher REE in infants with BPD compared with controls, suggesting that this could be one factor in the development of the malnutrition4–6. A variety of studies have attempted to answer the question as to whether or not preterm infants with chronic lung disease have higher rates of energy expenditure7–9. From the data presented, it is still difficult to come to a definitive conclusion about the elevation of energy expenditure in these infants. The purpose of this study was to determine whether or not the pulmonary status of children who had BPD presenting in the neonatal period is associated with a higher REE and poor nutritional status at a later age.

Patients and methods

Subjects included in this study were seventy-one children aged 4–8 years with prematurely-associated BPD (34 boys and 37 girls) and thirty healthy children (20 boys and 10 girls). The characteristics of the subjects are reported in Table 1. Neonatal characteristics of children with history of BPD are summarized in Table 2.

At 36 weeks post-conceptional age, all infants with BPD required additional oxygen therapy to correct hypoxemia, had clinical signs of chronic respiratory distress and had an abnormal chest radiograph10,11. Body composition was assessed by bioimpedance measurements to evaluate fat...
mass (FM) and fat-free mass (FFM). Pulmonary function was also assessed by measuring airway resistance (R). The study was approved by the Lille University Ethical Independent Committee and written informed consent was obtained from parents.

**Measurements**

**Auxologic characteristics**

Body weight and height were measured without shoes whilst wearing light indoor clothing. To determine body weight, a standard precision hospital scale was used for all measurements. Height was measured using a wall-mounted stadiometer. BMI was calculated as weight divided by height squared (kg/m²). Growth measurements were converted to Z scores relative to the French growth references of Sempé et al.12. The Z score was computed by taking the predicted value for the child’s age (for Z score weight for age) or for the child’s height (for Z score weight for height) and sex from the child’s measurements, and dividing the difference by the standard deviation of the measurement in the reference group.

**Resting energy expenditure**

On the day of the test, each child arrived at the Clinical Investigation Centre by car. Subjects had fasted for 10–12 h from the previous day and were not treated with β-agonic drugs or theophiline before the test. Weight and height were measured first. The child then rested, recumbent on a hospital bed, for 15 min. REE was measured by indirect calorimetry, using an open-circuit ventilated hood system (Deltatrac II, Datex Instrumentation Corporation, Helsinki, Finland). The RQ and flow settings were calibrated, by reference to alcohol combustion every 6 months and with a reference gas mixture (95% O₂, 5% CO₂), before each measurement. Inspired O₂ flow (VₐO₂), expired CO₂ flow (VₐCO₂) and the RQ were noted. REE was calculated every minute from O₂ consumption (VₐO₂ in ml/min), as was production of CO₂ (VₐCO₂ in ml/min) using the Weir formula without protein correction13. After an adaptation period of 15 min under a transparent canopy system, continuous respiratory exchange measurements were initiated. The measurements were conducted for a minimum period of 30 min. CV were, 10% for VₐO₂ and dilution airflow, and 5% for RQ.

**Bioimpedance analysis**

Bioimpedance analysis was done with a RJL-101 analyser (BIA 101S, 5RJL System, Akern, Detroit MI, USA) using an alternating current of 800 mA and 50 kHz. The measurements were standardized (supine, empty bladder, after 10–12 h fasting). The electrodes were placed at defined positions on the right wrist and ankle. The mean of three sequential readings was

<table>
<thead>
<tr>
<th>Table 1. Anthropometric characteristics of the children</th>
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<tbody>
<tr>
<td><strong>BPD (n 71)</strong></td>
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<tr>
<td>Mean</td>
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<tr>
<td>Age (years)</td>
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<td>Weight (kg)</td>
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<td>Height (cm)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>Sex ratio (M:F)</td>
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BPD, bronchopulmonary dysplasia; M, male; F, female

<table>
<thead>
<tr>
<th>Table 2. Neonatal characteristics of children with bronchopulmonary dysplasia (BPD)</th>
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<tr>
<td><strong>Total population with BPD (n 71)</strong></td>
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<tr>
<td>Mean</td>
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<tr>
<td>Birth weight (g)</td>
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<td>Gestational age (week)</td>
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<td>Weight at discharge (g)</td>
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<td>Weight at 40 weeks PMA(g)</td>
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<tr>
<td>Hospitalization duration (d)</td>
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<tr>
<td>Total ventilation (d)</td>
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<tr>
<td>Tracheal intubation (d)</td>
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<td>High-frequency oscillation ventilation (d)</td>
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<td>O₂ therapy duration (d)</td>
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<tr>
<td>Intra-uterine growth retardation (n)</td>
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<tr>
<td>Maternal–fetal infection (n)</td>
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<td>Twins (n)</td>
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<tr>
<td>Gastro-esophageal reflux (n)</td>
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<tr>
<td>Esophagitis (n)</td>
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<tr>
<td>Neonatal leus (n)</td>
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<tr>
<td>Patent ductus arteriosus (n)</td>
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<tr>
<td>Intra-ventricular ha emorrhage (n)</td>
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<tr>
<td>Neurological abnormalities at 2 years of age (n)</td>
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PMA, post-menstrual age.
used as the measurement value for the resistance (R). The Houtkooper formula\textsuperscript{14} estimates the FFM:

\[
FFM = 0.61RI + 0.25W
\]

\[
RI = H/2r, \text{ where } H \text{ is height (cm) and } W \text{ is weight (kg)}.
\]

FM was deduced as:

\[
FM = W - FFM
\]

where W is weight (kg) and FFM is fat-free-mass in kg. We previously demonstrated that impedanceometry provides a good estimation of body composition in this population when compared to total body absorptiometry\textsuperscript{16}.

**Energy intake**

An alimentary inventory using a 7-d food questionnaire was performed in all the patients. Data were analyzed with BILNUT 3 software (Nutrisoft, Paris, France) using updated national food tables.

**Pulmonary function tests**

All pulmonary function tests were performed after bronchodilators had been stopped for at least 2 weeks. R was measured by interruption of the airflow (software Dyn\textsuperscript{R} R, Paris, France); seven measurements were performed. A variation <14% was needed to validate the results. Functional residual capacity was measured by the dilution of He according to American Thoracic Society standards (Medisoft, Bruxelle, Belgium); this technique required two measurements with a variation of <10% to validate the results. The spirometry flow–volume curve, forced expiratory volume in 1 s (FEV\textsubscript{1}), and forced expiratory flow 25 to 75% vital capacity (FEF\textsubscript{25–75}) were evaluated. Five reproducible spirometry–flow volume curves (<10%) were necessary to validate the data.

Values were expressed as the percentage of the predicted value normalized for height and sex. R < 150%, FEV\textsubscript{1} > 80%, and FEF\textsubscript{25–75} > 80% were considered within the normal ranges. Proximal obstruction airflow was defined as R > 150% or FEV\textsubscript{1} < 80%. We assumed a maximal expiratory flow–volume loop with a marked concavity and FEF\textsubscript{25–75} < 80% to demonstrate distal flow limitation during spirometry.

**Predicted resting energy expenditure**

The Schofield Default\textsuperscript{17} was used to predict REE. Predicted REE was calculated for all the children and compared to the REE measured by indirect calorimetry.

**Statistical analysis**

Analyses were conducted to evaluate the impact of airway obstruction on REE and nutritional status in BPD. The population of children with BPD was divided into three groups: children without obstruction of the airways (R < 150% of normal, and FEV\textsubscript{1} > 80%, and normal maximal expiratory flow–volume loop and FEF\textsubscript{25–75} > 80%); children with moderate obstruction of the airways (R = 150–200% of normal, and/or FEV\textsubscript{1} < 80% and/or maximal expiratory flow–volume loop with a marked concavity and/or FEF\textsubscript{25–75} < 80%); and children with severe obstruction (R > 200% of normal and FEV\textsubscript{1} < 80%, and maximal expiratory flow–volume loop with a marked concavity and FEF\textsubscript{25–75} < 80%).

Fisher or \(X^2\) tests were used to compare qualitative data. The Mann–Whitney test was used to compare quantitative data. Values of \(P < 0.05\) were considered to be significant in all two-sided tests. The relation between REE and FFM has a significant intercept resulting in higher values for REE/FFM or REE/weight of subjects with a smaller FFM or smaller weight\textsuperscript{18}. A multivariate regression analysis was therefore performed on the parameters REE, FFM and weight to balance REE for weight and FFM.

**Results**

**Functional respiratory tests**

Forty-eight children with history of BPD (67.6%) presented with obstruction of the airways (R > 150% or FEV\textsubscript{1} < 80% or maximal expiratory flow–volume loop with a marked concavity and FEF\textsubscript{25–75} < 80%). Twenty-one children (29.5%) had moderate obstruction (R < 200% and/or FEV\textsubscript{1} < 80%, and maximal expiratory flow–volume loop with a marked concavity and FEF\textsubscript{25–75} < 80%) that was reversible by salbutamol in eleven cases. Seven children (9.8%) had severe obstruction (R > 200% of normal and FEV\textsubscript{1} < 80%, and maximal expiratory flow–volume loop with a marked concavity and FEF\textsubscript{25–75} < 80%), that was reversible in one case. Neonatal characteristics of the three groups are summarized in Table 2. No statistical difference was observed in neonatal characteristics between the three groups (\(P > 0.05\)).

Among children with severe obstruction of the airways, two received inhaled steroids before the age of 2 years and one received inhaled steroids until the age of 3 years. Among children with moderate obstruction of the airways, eleven received inhaled steroids before the age of 2 years; five received inhaled steroids until the age of 3 years and were still being treated with inhaled steroids at the time of the study. Among children without obstruction of the airways, eleven children received inhaled steroids before the age of 2 years, five received inhaled steroids until the age of 3 years and two were still being treated with inhaled steroids at the time of the study.

**Body composition and nutritional status**

Z scores of weight for age and weight for height, and BMI of children with BPD with moderate to severe obstruction were significantly lower than those of healthy control children (Table 3). There was no difference in Z scores of weight for height or weight for age or BMI in children with BPD without obstruction when compared to controls.

Z scores of weight for age and weight for height, BMI, FM, and FFM of children with BPD with severe obstruction were not significantly different from the scores of those with BPD but without obstruction. A significant decrease of FM was observed in children with BPD with severe airway obstruction while those with BPD with moderate airway obstruction or without obstruction did not demonstrate any significant change in their body composition compared with healthy children (Table 3).
Despite advances in neonatal critical care, including reduced 
(Table 4).
significantly different in BDP groups compared to controls 
the control group.
lower in the group of children with BPD when compared to 
when corrected for weight or FFM, REE was not significantly 
outcome than those related to pulmonary disease 21. Conver-
factors may be even more important contributors to eventual 
status in later childhood (lower BMI, lower Z scores of weight 
and weight for height, and reduced FM in cases of 
status in these children compared with chil-
dren4,24. There are several reasons for this difference: 
higher values of REE in children with BPD could 
the poorer nutritional status in these children compared with chil-
dren with BPD without obstruction. Nevertheless measured 
REE was not higher than predicted REE in children with 
BPD, and was not higher in the group with severe airway 
obstruction after weight or FFM adjustment. However, since 
only seven children suffered from severe obstruction of the 
airways, that represents a study limitation when analyzing 
factors associated with pulmonary sequel in BPD. It has 
been shown that treatment with β-adrenergic drugs or 
theophylline, which our patients with BPD had previously 
used, increased O2 consumption and therefore could explain 
the high REE in these patients 22,23. To minimize this effect 
however, all these drugs were stopped several days before 
REE was measured in our patients.

Resting energy expenditure and energy intakes
Measured REE and the REE predicted by the Schofield 
 equation were significantly lower in children with BPD 
(P < 0.001, Table 4) when compared to controls. However, 
when corrected for weight or FFM, REE was not significantly 
lower in the group of children with BPD when compared to 
the control group.

There was not a significant difference between measured 
and predicted REE in any groups. Energy intakes were not 
significantly different in BDP groups compared to controls 
(Table 4).

Discussion
Despite advances in neonatal critical care, including reduced 
O2 concentrations and less traumatic ventilatory therapies, 
BPD still affects one third of very low-birth-weight preterm 
infants 19. Earlier reports of survivors of BPD highlighted 
delays in growth and development in the first few years of 
life, but limited data are available on the long-term outcome 
of older children with BPD 20–22. Several research groups 
have attempted to answer the question as to whether or not 
the higher values of REE in children with BPD could 
contribute to a poor nutritional status. Giacoia and co-workers 
investigated the outcome of school-age children with BPD 
in terms of nutrition, pulmonary function, REE, body 
composition, and intelligence. The results were compared 
with a preterm cohort matched for gestational age and birth 
weight, and with a term control group 22. As in our study, 
they did not find any difference in the REE between children 
with BPD and controls. Their results on growth and mental 
ability support previous observations that premature-related 
actors may be even more important contributors to eventual 
outcome than those related to pulmonary disease 21. Conver-
sely, our study shows that the pulmonary status of children 
with BPD seemed to be associated with an altered nutritional 
status in later childhood (lower BMI, lower Z scores of weight 
for age and weight for height, and reduced FM in cases of 
airway obstruction). Increased REE could contribute to the 
poorer nutritional status in these children compared with chil-
dren with BPD without obstruction. Nevertheless measured 
REE was not higher than predicted REE in children with 
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however, all these drugs were stopped several days before 
REE was measured in our patients.

A few studies have demonstrated that during the neonatal 
period children with BPD have a higher REE than healthy chil-
dren 22,23. There are several reasons for this difference: 
an increase in the work involved in breathing, inflammation 
and/or infection, and a different body composition with 
consistent decrease of FM and increased metabolically active 
FFM 24,25. In adults with chronic pulmonary obstructive

Table 3. Comparison of auxologic characteristics of children with bronchopulmonary dysplasia (BPD) with severe, or moderate obstruction of the airways or without pulmonary sequelae with healthy children (controls)

<table>
<thead>
<tr>
<th></th>
<th>BPD without airway obstruction (n 43)</th>
<th>BPD with moderate obstruction (n 21)</th>
<th>BPD with severe obstruction (n 7)</th>
<th>Controls (n 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z score of weight for age</td>
<td>-0.6 ± 1.6, P &gt; 0.05</td>
<td>-1.1 ± 1.4, &lt; 0.05</td>
<td>-1.2 ± 1.0, &lt; 0.05</td>
<td>0.2 ± 0.8</td>
</tr>
<tr>
<td>Z score of height for age</td>
<td>-0.5 ± 1.4, NS</td>
<td>-0.4 ± 1.1, NS</td>
<td>-0.4 ± 1.4, NS</td>
<td>0.4 ± 0.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.0 ± 1.8, NS</td>
<td>14.0 ± 0.3, &lt; 0.05</td>
<td>15.5 ± 1.3, &lt; 0.001</td>
<td>17.5 ± 2.1</td>
</tr>
<tr>
<td>Z score of height for height</td>
<td>-0.5 ± 1.6, NS</td>
<td>-0.9 ± 0.3, &lt; 0.05</td>
<td>-1.78 ± 1.6, &lt; 0.05</td>
<td>0.1 ± 1.1</td>
</tr>
<tr>
<td>Fat mass (% of weight)</td>
<td>17.0 ± 10.0, NS</td>
<td>17.0 ± 20.0, NS</td>
<td>10.0 ± 3.5, &lt; 0.001</td>
<td>17.0 ± 8.0</td>
</tr>
</tbody>
</table>

Table 4. Comparison of REE and energy intakes of children with bronchopulmonary dysplasia (BPD) with severe or moderate obstruction of the airways or without pulmonary sequelae with healthy children (controls)

<table>
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</thead>
<tbody>
<tr>
<td>REE (kJ/d)</td>
<td>3855 ± 693, &lt; 0.05</td>
<td>3805 ± 483, &lt; 0.05</td>
<td>4116 ± 411, &lt; 0.05</td>
<td>4578 ± 907</td>
</tr>
<tr>
<td>Schofield (kJ/d)</td>
<td>3675 ± 310, &lt; 0.05</td>
<td>3755 ± 306, &lt; 0.001</td>
<td>3780 ± 172, &lt; 0.001</td>
<td>4595 ± 932</td>
</tr>
<tr>
<td>REE/Schofield (%)</td>
<td>107 ± 8.7, NS</td>
<td>106 ± 10.0, NS</td>
<td>108 ± 7.0, NS</td>
<td>106 ± 11.0</td>
</tr>
<tr>
<td>Energy intakes/weight (kJ/kg per d)</td>
<td>426 ± 176, NS</td>
<td>450 ± 134, NS</td>
<td>421 ± 152, NS</td>
<td>416 ± 157</td>
</tr>
</tbody>
</table>

Schofield, REE predicted by the Schofield equation.
disease, REE was found to be positively correlated with pulmonary illness. Patients with chronic obstructive pulmonary disease have increased respiratory muscle energy consumption secondary to an increased resistive load and impaired efficiency of the respiratory muscle. REE is known to be correlated with weight, height, age, sex, FFM or FM in both adults and children. The best predictor of REE in childhood is FFM, which represents the tissues with the highest metabolic activity. Tissues containing FFM have various degrees of metabolic activity. Organs such as the brain, liver, heart, and kidneys are made of cells with high energy expenditure levels (> 60% of REE). Muscles have a lower metabolic rate (30% of REE). Children with BPD, like other children with chronic obstructive pulmonary disease, have been reported to have growth failure and a decreased FM. When malnutrition occurs, the body alters the ratio of loss of body fat to muscle mass, but the highly metabolic tissues of the vital organs (brain, heart, liver and kidneys) are conserved. Although the body composition methods used in our study did not allow precise analysis of such highly metabolically active tissues, we did not observe any increase in REE suggesting an alteration of metabolically active tissues in children with BPD. Other factors such as chronic inflammation could also increase REE in children with a history of BPD. During the neonatal period, O2 therapy may induce lung injuries, by volo- or baro-traumatism, which may then contribute to BPD lesions. Early inflammation and angiogenic responses interfere with lung development and prevent alveolar growth. During the first few years of life, recurrent infections maintain inflammation. Children with BPD tend to present with an increased incidence of recurrent infections of the lower respiratory tract (bronchiolitis and pneumonia) up to 2 years old that contributes to the persistence of lung inflammation and increases hospital admissions. Our results did not support such a hypothesis of lung or general inflammation in the long term for children with BPD.

In a previous study we showed that undernutrition was not correlated with pulmonary status in later childhood, but that both were associated with nutritional status before the age of 2 years. After this period, undernutrition and hyperinflation of the airways seem to be fixed sequelae and independent features. In children who had bronchopulmonary dysplasia in infancy, nutritional status at 2 years of age could influence both nutrition and pulmonary outcomes in childhood. The present study supports the hypothesis that body composition and pulmonary function in BPD in later childhood are fixed sequelae originating from the neonatal period.

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References


