Airway Function Measurements and the Long-Term Follow-Up of Survivors of Preterm Birth With and Without Chronic Lung Disease

Indra Narang, MRCPCH, Eugenio Baraldi, MD, Michael Silverman, MD, FRCP, FRCPCH, and Andrew Bush, MD, FRCP, FRCPCH

Summary. This seventh paper in a review series on different aspects of chronic lung disease following preterm birth focuses on the current knowledge of respiratory symptoms, airway function, airway hyperresponsiveness, and exercise capacity from childhood to adulthood. This paper further considers the long-term implications of these studies for both future research and clinical practice. Pediatr Pulmonol. 2006; 41:497–508. © 2006 Wiley-Liss, Inc.

Key words: preterm infant; bronchopulmonary dysplasia; cough; wheeze; asthma lung function; airway hyperresponsiveness; exercise tolerance.

INTRODUCTION

This is the seventh paper in a review series that has summarized the available data and discussed the respiratory morbidity of survivors of low birth weight, preterm birth.

Preterm birth occurs during a vulnerable period of lung maturation. The clinical outcomes of such infants are determined by not only the circulatory and gas-exchange capacity of the lungs at birth, but also by necessary medical interventions which include oxygen therapy and intermittent positive pressure ventilation (IPPV).

The resulting pulmonary sequelae of preterm babies, if severe enough, may include bronchopulmonary dysplasia (BPD), first described by Northway et al. in 1967. With the introduction of surfactant therapy and the implementation of lung-protective strategies, there is increased survival of the more immature neonate. However, the prevalence of pulmonary sequelae has not declined, as could have been expected from improved management, thus increasing the burden of respiratory healthcare delivery.

This paper reviews what is known about the respiratory morbidity of survivors of BPD, focusing on mid-childhood into early adult life. A full comprehensive review of BPD in infancy, including pathophysiology and clinical management, can be found elsewhere. The long-term implications of BPD and the need to follow up into adulthood are briefly discussed. Finally, we speculate on the implications of “new” BPD and future work in this group of subjects.

© 2006 Wiley-Liss, Inc.
following treatment for RDS in preterm infants. For the purposes of this review, the term BPD will be used in preference to CLD of prematurity, to distinguish it from all other forms of CLDI.

There are crucial factors which are implicated in the pathogenesis of BPD. Preterm birth per se may result in the interruption of normal alveolar development. Further, those treatments that are necessary for survival of the preterm infant may prevent further normal alveolar development, e.g., mechanical ventilation and oxygen therapy. BPD was initially defined as the need for supplemental oxygen at 28 days of postnatal age in preterm infants who required mechanical ventilation for at least 1 week, who had symptoms of persistent respiratory distress, and who had x-ray studies of the chest which showed radiolucent areas alternating with radiodense areas. However, BPD today (the “new” BPD, as discussed later in this review) is different from the BPD described nearly 40 years ago, as birth of extremely immature infants can result in an interruption of alveolarization at a very early stage, with subsequent alveolar-capillary hypoplasia. The recently proposed definition of BPD, or CLD of prematurity, is diagnosis after 28 days of persisting oxygen dependency, followed by severity grading at 36 weeks of postconceptual age for infants born at gestational ages of less than 32 weeks.

Unless specifically indicated, the old definition of BPD is used in this paper.

**GENERAL METHODOLOGICAL PROBLEMS**

Comparisons between studies are often difficult because of the disparate populations studied, and the different treatments used, including different modes of ventilation, and the use or otherwise of ante- and postnatal steroids, and surfactant. Factors other than prematurity and its treatment may also be significant in producing symptoms, including atopy, passive tobacco-smoke exposure, social class, and family history. It is virtually impossible to unravel the relationship between these factors and (1) the increased likelihood of prematurity and birth weight, (2) the effects on the severity of neonatal respiratory illness for a given degree of prematurity and reduction in birth weight, and (3) any independent postnatal effects on airway health. For example, maternal smoking is associated with low birth weight and prematurity, and also increased postnatal respiratory symptoms in term babies. Thus, defining the precise contributions of smoking and prematurity per se is very difficult.

The choice of a control population is critical. The ideal longitudinal study would recruit and retain a contemporaneous control group, well-matched for relevant confounding variables. In practice, it is hard enough to retain the patient group over time, let alone normals, and no one has in practice achieved this study. More than one control group would be ideal, including term healthy controls and preterm controls requiring varying degrees of neonatal intervention.

The other obvious difference between cohort studies in the BPD population, and the great cohort studies which have taught us so much about infant wheezing phenotypes, is that prematurity is unpredictable and relatively uncommon, so antenatal recruitment is not possible. Thus antenatal factors have to be gathered retrospectively, with all the problems that entails. The matching of controls and subjects is also problematic: careful matching is ideal, but often not possible. In general, these difficulties have led to the pragmatic selection of population controls, recruited at time of...
follow-up of the BPD subjects, in the hope that the new controls are not too dissimilar from the term population at the time of delivery of the BPD cohort.

There is also the issue of selection bias. By definition, many preterm babies are not followed up either because they have died, or suffered severe neurological injury and cannot participate in the study. Adult BPD survivors in particular represent a highly selected group, from an era when the mortality of BPD was at least 40%. Survivors may also have coincident comorbidity such as reflux or dysfunctional swallowing, which may contribute independently to respiratory morbidity. Thus follow-up studies probably report on the “good” end of the preterm spectrum.

Finally, the word “asthma” is often loosely used in follow-up studies, and frequently not defined. The mere presence of wheeze does not prove the presence of atopic airway inflammation. Although BPD and asthma share some clinical and functional features, there is recent evidence to suggest that, unlike children with asthma, school-age survivors of BPD have airflow limitation associated with low exhaled Nitric oxide [eNO] values, suggesting that airflow limitation was not related to asthma-like inflammation, perhaps indicating a difference in the underlying pathophysiology of the two obstructive lung diseases. Authors should thus avoid the term asthma, or else define it rigorously.

**THE MEDIUM AND LONG-TERM EFFECTS OF BPD**

Unless indicated otherwise, the studies described are from the presurfactant era.

**Respiratory Symptoms**

The results of larger studies reporting respiratory symptoms in childhood are summarized in Table 1. Small studies, reporting less than 30 children, were excluded, although including them does not significantly alter the conclusions.

**Mid-childhood**

In mid-childhood (defined here as ages 5–12 years), prematurity is associated with an excess of respiratory symptoms (surfactant administered in the study by Palta et al. in both low birth weight (LBW, 1,500–2,000 g) and very low birth weight (VLBW, <1,500 g) subjects, even if as a baby, respiratory support was minimal. There are trends for symptoms to be more severe if the baby required prolonged ventilation, or developed BPD.

**Adolescence**

The situation in adolescence (defined here as >12 years of age) is less clear-cut. Doyle et al. compared preterm children with term controls (n = 42), and found no difference in respiratory health. By contrast, Anand et al. found significantly higher rates of chronic cough, wheezing, and “asthma” (not defined), which were associated with airflow obstruction in the VLBW population compared with controls. However, the prevalence of “asthma” was similar in both studies, at 15% and 21% in the LBW and VLBW groups, respectively, and 18% in Anand et al. There were differences in the reported prevalence of asthma among controls, underscoring the need for care in choosing the correct control population. Only 6% of the controls in Anand et al. reported asthma, in keeping with reported median (range) population values of 4.5 (2.0–11.0). However, 21% of the controls in Doyle et al. had “asthma.” The lack of concordance in these studies may also be attributed to the fact that one study was hospital-specific, and the other represented a more heterogeneous sample.

**TABLE 1—Large Studies (Defined as ≥100 Subjects and Controls) Seeking Associations Between Prematurity, Low Birth Weight, Their Treatment, and Subsequent Reported Respiratory Morbidity**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (years)</th>
<th>No. S</th>
<th>BW/Gest</th>
<th>No. C</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenough et al., 1996</td>
<td>5</td>
<td>103</td>
<td>29 weeks</td>
<td>None</td>
<td>Symptom diary, clinical review</td>
<td>30% symptomatic; worse with more prolonged O2, IPPV</td>
</tr>
<tr>
<td>McLeod et al., 1996</td>
<td>8–9</td>
<td>300</td>
<td>VLBW</td>
<td>590</td>
<td>Questionnaire</td>
<td>More cough, hospital admissions; no neonatal associations sought</td>
</tr>
<tr>
<td>Palta et al., 2001</td>
<td>8</td>
<td>384</td>
<td>VLBW</td>
<td>154</td>
<td>ISAAC questionnaire</td>
<td>Excess symptoms and wheeze, particularly if BPD</td>
</tr>
<tr>
<td>Rona et al., 1993</td>
<td>6–11</td>
<td>5,500</td>
<td>All BW and Gest</td>
<td>None</td>
<td>Questionnaire</td>
<td>Excess wheeze with prematurity, not BW</td>
</tr>
<tr>
<td>Chan et al., 1989</td>
<td>7–9</td>
<td>121</td>
<td>LBW and VLBW</td>
<td>100</td>
<td>Questionnaire</td>
<td>More cough, even if only O2 therapy, more wheeze</td>
</tr>
<tr>
<td>Doyle et al., 2001</td>
<td>14</td>
<td>180</td>
<td>&lt;30/40</td>
<td>42</td>
<td>Clinical review</td>
<td>No increase in symptoms</td>
</tr>
<tr>
<td>Anand et al., 2003</td>
<td>15</td>
<td>128</td>
<td>VLBW</td>
<td>128</td>
<td>Questionnaire</td>
<td>More cough, wheeze, and “asthma,” irrespective of BPD</td>
</tr>
</tbody>
</table>

No. S, number of subjects; No. C, number of controls; Gest, gestation; BW, birth weight.
Young Adults

Northway et al.\textsuperscript{23} studied a group of young adults (mean age, 18.3 years) with a previous history of BPD. They had a history of more wheezing, episodes of pneumonia, and long-term medication use when compared with nonventilated BPD babies. Respiratory symptoms persisted in 6/26 (23\%) subjects.

Specific Methodological Problems

There are many methodological problems with the published data. Only the ISAAC questionnaire\textsuperscript{24} was rigorously validated, and the sensitivity, reproducibility, and validity of the other questionnaires are not known. There has been no attempt to validate the difficult symptom “wheeze,” a term which can be notoriously ambiguous.\textsuperscript{25–27} The term “asthma” is also used very imprecisely, and usually means that someone thought the child had recurrent noises that were interpreted as wheeze. No objective cough monitoring was performed.\textsuperscript{28–30}

Respiratory Symptoms and the Effects of Surfactant

The studies referred to above were undertaken in the presurfactant era. Sell et al.\textsuperscript{31} studied children whose birth weight was between 700–1,100 g, who were entered into a multicenter, parallel, randomized, double-blind, placebo-controlled trial of synthetic surfactant. The incidence of “asthma” at age 1 year was significantly higher in the group of infants given placebo: 10\%, vs. 4\% for surfactant. This effect was lost in a small follow-up in older children.\textsuperscript{32}

Summary

There are more respiratory symptoms in infancy and childhood in those who were born preterm. The risk factors are not completely clear, but probably include birth weight independent of any other factor, mechanical ventilation, a family history of atopy, and BPD. The balance of the evidence is that there is improvement with age, but in those who had a particularly severe neonatal course, there is some evidence that these symptoms may persist into adolescence and adulthood.

LUNG FUNCTION STUDIES

Cross-Sectional Lung Function Studies

Since there are fewer large studies assessing lung function than those that describe respiratory symptoms in the ex-preterm subject, both large and relevant smaller studies will be described here (and see Table 2).

Midchildhood

McLeod et al.\textsuperscript{17} found that in VLBW children, a forced expired volume in 1 sec (FEV\textsubscript{1}) to forced vital capacity (FVC) ratio (FEV\textsubscript{1}/FVC) of less than 70\% was significantly associated with duration of IPPV that was greater than 28 days ($P < 0.05$), prolonged use of oxygen therapy ($P < 0.005$), and RDS ($P < 0.01$). Birth weight was not an independent risk factor. These study subjects represent a very heterogeneous group, as they were treated in many different centers with different treatment protocols. Kitchen et al.\textsuperscript{33} examined an earlier VLBW cohort. They found that FEV\textsubscript{1} and FVC were unrelated to BPD and to

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (years)</th>
<th>No. S</th>
<th>BW/Gest</th>
<th>No. C</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLeod et al., 1996\textsuperscript{17}</td>
<td>8–9</td>
<td>300</td>
<td>VLBW</td>
<td>590</td>
<td>Spirometry</td>
<td>Airflow obstruction, BW not a risk factor</td>
</tr>
<tr>
<td>Kitchen et al., 1992\textsuperscript{33}</td>
<td>8</td>
<td>210</td>
<td>VLBW</td>
<td>None</td>
<td>Spirometry</td>
<td>No effect of neonatal events</td>
</tr>
<tr>
<td>Chan et al., 1989\textsuperscript{34}</td>
<td>8–9</td>
<td>130</td>
<td>LBW and VLBW</td>
<td>120</td>
<td>Spirometry</td>
<td>BW a risk for airflow obstruction; dose effect for neonatal treatment</td>
</tr>
<tr>
<td>Anand et al., 2003\textsuperscript{31}</td>
<td>15</td>
<td>128</td>
<td>VLBW</td>
<td>128</td>
<td>Spirometry</td>
<td>MEF\textsubscript{25–75} reduced in VLBW</td>
</tr>
<tr>
<td>Doyle et al., 2001\textsuperscript{30}</td>
<td>14</td>
<td>180</td>
<td>LBW and VLBW</td>
<td>42</td>
<td>Spirometry</td>
<td>BPD had reduced FEV\textsubscript{1} and FEV\textsubscript{1}/FVC</td>
</tr>
<tr>
<td>Northway et al., 1990\textsuperscript{33}</td>
<td>14–23</td>
<td>26</td>
<td>BPD</td>
<td>26</td>
<td>Spirometry, plethysmography</td>
<td>Airway obstruction in BPD</td>
</tr>
<tr>
<td>Chan et al., 1990\textsuperscript{30}</td>
<td>9</td>
<td>27</td>
<td>VLBW</td>
<td>46</td>
<td>Plethysmography</td>
<td>Reduction in spirometry</td>
</tr>
<tr>
<td>Parat et al., 1995\textsuperscript{36}</td>
<td>8</td>
<td>13</td>
<td>BPD</td>
<td>7, no BPD</td>
<td>Spirometry</td>
<td>FEV\textsubscript{1}, no-BPD &gt; BPD</td>
</tr>
<tr>
<td>Mitchell et al., 1998\textsuperscript{35}</td>
<td>10–12</td>
<td>10</td>
<td>BPD</td>
<td>10 term 10</td>
<td>Spirometry</td>
<td>FEV\textsubscript{1}, terms &gt; healthy preterms &gt; BPD</td>
</tr>
</tbody>
</table>

\textsuperscript{1}No. S, number of subjects; No. C, number of controls; Gest, gestation; BW, birth weight.
IPPV; abnormalities of flow rates were only seen in those with asthma or recurrent bronchitis at 8 years of age. However, this study was uncontrolled, and so there was a reliance on published reference values for lung function. The Hammersmith cohort, recruited from birth, was also followed up in mid-childhood. The mean FVC was the same as in controls, but the forced expired volume in 0.75 sec (FEV$_{0.75}$), forced expiratory flow at 25%, 50%, and 75% of forced vital capacity (FEF$_{25}$, FEF$_{50}$, and FEF$_{75}$, respectively), and FEF$_{0.75}$/FVC were significantly lower in the study group compared with controls ($P < 0.001$ for all parameters). Airway function strongly correlated with birth weight ($P < 0.0001$) and to a lesser extent with gestational age ($P < 0.05$), irrespective of the neonatal course. This cohort was further subdivided into four groups: those who had no neonatal illness ($n = 68$), those who received oxygen only ($n = 25$), those who required IPPV ($n = 27$), and those who had BPD in infancy ($n = 10$). Overall, the children who had received any neonatal treatment had poorer airway function than those who had not. There was, however, no difference between those who received oxygen treatment alone and those who received IPPV in addition. Among those who received oxygen treatment and additional IPPV, there was no correlation between oxygen therapy, duration or peak inspiratory pressure of IPPV, and subsequent airway function. Other associations with poorer airway function were male sex and maternal smoking. The subgroup with BPD also showed reduced FVC as well as other airway function indices.

In two small studies, children with BPD were compared with ex-preterm children who did not have a history of BPD and term controls. The BPD and ex-preterm groups all had birth weights <1,500 g and were at <34 weeks of gestation. The BPD and preterm groups had a mean lower FEV$_1$ when compared with predicted normal values. Thus, BPD, but also preterm birth alone, were risk factors for airway obstruction in mid-childhood. The impact of other risk factors could not be ascertained, as no history of prenatal or postnatal treatment with steroids, or exposure to environmental tobacco smoke (ETS), was sought in these studies. The impact of surfactant was addressed by Gappa et al. in a study of 69 children who had been randomized to receive either surfactant ($n = 34$) or placebo ($n = 35$). Survival without BPD was significantly higher in surfactant-treated patients infants (26/34) compared with controls (14/35). At 6 years of postnatal age, there were no differences in spirometry, possibly because the study was underpowered.

Adolescence and Adulthood

Very few studies have assessed lung function in adolescence. Whether “catch-up” growth occurs is controversial. Anand et al. adjusted for self-reported smoking in both the subjects and their mothers, and found a reduction in forced midexpiratory flow between 25–75% of FVC (FEF$_{25–75}$) in VLBW compared with controls, suggesting distal airflow obstruction which was not associated with either low birth weight or respiratory support. The implication was that catch-up growth had not occurred. The authors concluded that the key risk factor is preterm birth. However, while this may be true, no further treatment history was given of these subjects. Doyle et al. found that lung function was mostly normal in their three groups (term, LBW, and VLBW), although a significantly greater proportion of children with BPD had a clinically important reduction in their FEV$_1$ and FEV$_1$/FVC ratios compared with those preterm children without BPD. It is of interest that the mean percent predicted FEF$_{25–75}$ in Doyle et al. was lower than that of the VLBW group studied by Anand et al.. The different conclusions may be due to the different reference values used, again underscoring the need for appropriate controls.

In the longest follow-up to date, Northway et al. found that the mean percent predicted FEV$_1$, FVC, and FEV$_{25–75}$ were significantly lower in the BPD group compared with the preterm and term controls. Airway resistance (Raw) was higher, and specific conductance (sGaw) was lower, with more marked hyperinflation in the BPD cohort compared with the other groups. BPD was considered the major risk factor for reduced airflow, as there was no apparent association with neonatal variables. However, the small numbers of subjects, relatively high birth weights (mean, >1,800 g), and maturity (mean gestational age, >33 weeks) in the BPD preterm groups may have resulted in the lack of any association. It must also be borne in mind that in the present day, those considered to be at high risk of respiratory morbidity probably did not survive in the late 1960s.

Longitudinal Lung-Function Studies

Only a few studies have assessed lung function longitudinally, beyond preschool years in ex-preterm survivors (Table 3). Filippone et al. followed a group of moderate to severe BPD children (surfactant-treated) from birth to midchildhood, and measured maximal flow at functional residual capacity ($V\'maxFRC$) at 2 years of age, and spirometry at 8.8 years of age. Although the sample size was small, they showed that the degree of spirometric impairment at school age was closely related to the severity of airflow limitation found at age 2 years, consistent with tracking of airway function with time. The authors hypothesized that airflow limitation during infancy is an expression of early remodeling processes of the airways that persist into childhood. More detailed studies were performed on a subgroup of the Hammersmith cohort who were all VLBW (<1,500 g).
FEV₁ and FVC were significantly reduced in the VLBW group compared with controls ($P < 0.01$ for both). There was no significant difference in the FEV₁/FVC ratio and FEF₂₅₋₇₅. There was no significant correlation between dynamic lung compliance ($C_{L,dyn}$) recorded in the first 6 months of life and airway conductance (Gaw) recorded at age 9 years ($P < 0.05$). sGaw showed a direct association with the FVC and FEV₁/FVC ratio at age 9 years, and correlated inversely with the residual volume (RV)/TLC ratio. There was no association between Gaw and oxygen therapy or duration of IPPV during the first year. These results suggest that Gaw measured early in life is the best predictor of airway function later in life.

Blayney et al.⁴⁰ reported that mean total lung capacity (TLC) and functional residual capacity (FRC) were normal at both 7 and 10 years of age in 32 BPD subjects, but RV and the RV/TLC ratio were elevated at both ages. All subjects with a low FEV₁ at age 7 years showed an improvement in spirometry at age 10 years. Longitudinal studies extending beyond childhood are sparse. Doyle et al.⁴¹ assessed a large group of VLBW at ages 8.3 and 14.2 years. Spirometry was within normal range at age 8 years, but there was a significant increase by age 14 years. There was a decline in mean percent predicted FEF₂₅₋₇₅, possibly indicating the development of small airways disease during this time. RV and RV/TLC ratios were closer to normal predicted values at age 14 years. Forcing midexpiratory flows rates declined more in those with lower birth weights. Duration of IPPV, oxygen therapy, and BPD were not associated with significant differences in the rate of change in spirometry between 8 and 14 years. The authors did not look for associations between flow at low lung volumes, maternal smoking during pregnancy, and steroid administration, all of which may influence lung growth in utero. In a much smaller study ($n = 17$), Koumbourlis et al.⁴² measured spirometry at ages 8 and 15 years. They used their own definition of BPD as “any clinical, radiographic, or lung function abnormality that evolves during and persists beyond the neonatal period in preterm infants,” which describes a much more varied group than those with BPD diagnosed by conventional criteria.¹ Their main abnormal finding was a low mean percent predicted FEF₂₅₋₇₅ during visit 1, with little change 7 years later, indicating persistent airflow obstruction. Surprisingly, despite a small sample size, they described a relationship between tracking of lung function and duration of oxygen therapy and treatment with IPPV, but not with symptoms such as wheeze. Low FEF₂₅₋₇₅ was also associated with airway hyperresponsiveness (AHR) which was unrelated to a history of asthma, exposure to smoking, and lower respiratory tract infections in early childhood. TLC, vital capacity (VC), and FRC were normal at both ages. In contrast, RV decreased during the same period, resulting in normalization of RV/TLC ratios, especially in those subjects with significant degrees of airway obstruction. The authors concluded, despite having no normal longitudinal data on lung volumes in infancy, that “catch-up growth occurs in early childhood and proceeds normally thereafter.” These results can only be interpreted with caution.

**Summary**

While these studies are not conclusive, they suggest some improvement in pulmonary function with time. The pulmonary dysfunction observed in the adolescents and young adults who had BPD in infancy may not solely reflect the effects of neonatal BPD, as the impact of neonatal treatments, such as oxygen and mechanical ventilation, is

---

**TABLE 3— Longitudinal Studies of Lung Function After Preschool Years in Survivors of Prematurity, Low Birth Weight, and Neonatal Treatment¹**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (years)</th>
<th>No. S</th>
<th>BW/Gest</th>
<th>No. C</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filippone et al., 2003³⁸</td>
<td>2.0, 8.8</td>
<td>18,18</td>
<td>BPD</td>
<td>None</td>
<td>V’maxFRC Spirometry</td>
<td>V’maxFRC abnormal: FEV₁ and FEF₂₅₋₇₅ abnormal at 8 years, with evidence of tracking of lung function</td>
</tr>
<tr>
<td>Blayney et al., 1991⁴⁰</td>
<td>7.0, 10.0</td>
<td>32, 32</td>
<td>BPD</td>
<td>None</td>
<td>Spirometry, lung volumes</td>
<td>Airway obstruction, catch-up growth</td>
</tr>
<tr>
<td>Doyle et al., 1999⁴¹</td>
<td>8.3, 14.2</td>
<td>152, 152</td>
<td>VLBW</td>
<td>None</td>
<td>Spirometry, lung volumes</td>
<td>Age 8.3: normal spirometry, air trapping; age 14.2: even better spirometry, reduced air-trapping, declining midexpiratory flows</td>
</tr>
<tr>
<td>Chan et al., 1990³⁹</td>
<td>3, 6, and 12 months; 9 years</td>
<td>27 (10 BPD)</td>
<td>VLBW</td>
<td>None</td>
<td>Plethysmography, esophageal manometry, spirometry</td>
<td>Reduction in spirometry correlating with sGaw in early life Age 8.2: low MEF₂₅₋₇₅ and hyperinflation Age 15.1: low MEF₂₅₋₇₅ normal lung volumes</td>
</tr>
<tr>
<td>Koumbourlis et al., 1996⁴²</td>
<td>8.2, 15.1</td>
<td>17, 17</td>
<td>Preterm, LBW</td>
<td>None</td>
<td>Spirometry, lung volumes</td>
<td></td>
</tr>
</tbody>
</table>

¹No. S, number of subjects; No. C, number of controls; Gest, gestation; BW, birth weight.
less important as the child gets older. Other investigators demonstrated that BPD infants are particularly susceptible to lower respiratory illnesses in childhood, and that these may be related to chronic airflow obstruction in adulthood. Environmental influences such as tobacco smoke may also contribute to airflow obstruction.

However, an important consideration is whether the studies describing apparent normalization of lung function truly reflect a “catch-up” of lung growth. These studies may merely reflect a decreased sensitivity of spirometry in this age group. Further, spirometry has long been known to be insensitive to distal airflow obstruction until the very late phases. One could argue that spirometry should not be used as a marker of lung growth, and that the use of more sophisticated methods to assess lung ventilation and lung growth is necessary to provide more accurate information. Indices of overall ventilation inhomogeneity, such as the lung clearance index, are abnormal in many infants and young children with cystic fibrosis. These indices may be more sensitive than other lung function measures for the early detection of airflow disease. Additionally, the noninvasive assessment of lung growth with the use of labeled carbon monoxide and hyperpolarized gases in magnetic resonance may provide further answers.

What is clear, however, is that those subjects that demonstrate apparent normalisation of airway function following preterm birth will still require continued follow up into late adulthood in order to assess whether there is a premature decline in ventilatory function.

**Airway Hyperresponsiveness**

Atopy and AHR are associated (see Table 4), even in asymptomatic subjects. It is debated whether AHR, which was repeatedly reported to occur in long-term survivors of BPD, is a consequence of BPD or contributes to the pathophysiology of BPD in genetically predisposed patients following preterm birth. One study reported baseline spirometry which was significantly reduced in BPD and non-BPD groups compared with term controls, and the provocative dose of histamine to cause a 15% fall in FEV\(_1\) (PD\(_{15}\)) was lower in the BPD compared with the non-BPD preterm group. There was a strong association between respiratory symptoms and AHR. In young adults with a history of BPD, AHR was more prevalent in the BPD than the ex-preterm population but was not related to respiratory symptoms, atopy, or a family history of asthma.

In 122 of the Hammersmith cohort, increased AHR was seen in 71% of the index study group, compared with 43% of controls (P < 0.01). There was a significant association between a personal or family history of asthma and increased AHR in both the index study group and controls. Increased AHR in the index study group was observed more in those subjects with a positive skin-prick test to house dust mite, grass pollens, or cat fur (P < 0.01), although skin-prick tests were not performed in the control group. However, there was also an association between AHR and duration of oxygen treatment. To determine the pathophysiological basis for the increased prevalence of AHR in the index study group, 35 of the mothers of the index study group also underwent a histamine challenge. Using the same protocol, 8.6% mothers of the index study group had a PD\(_{15}\) (using histamine) of 3.9 μmol, which was similar to the 10.5% reported in an adult population using the same methods to determine AHR. In a second study, 15 subjects participated in a double-blind, placebo-controlled, crossover design with 4-week-long treatment periods with inhaled steroids or placebo. There was no significant difference in respiratory symptom score, baseline airway function, or airway response to histamine between the two treatment periods. From these studies, the authors concluded that abnormal AHR was related to abnormal pulmonary development and not to an effect of chronic inflammation or maternal factors. However, the authors assumed that that any preexisting inflammation would be steroid-sensitive, which may not necessarily be true.

**Summary**

In summary, there is no doubt that AHR is common in survivors of preterm birth. It is probable that it is

---

**TABLE 4—Studies of Airway Reactivity After Preschool Years in Survivors of Prematurity, Low Birth Weight, and Neonatal Treatment**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age (years)</th>
<th>No. S</th>
<th>BW/Gest</th>
<th>No. C</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelkonen et al., 1997</td>
<td>8–14</td>
<td>12 BPD</td>
<td>BW &lt;1.25 kg, Gest &lt;27/40</td>
<td>17 preterm, no-BPD</td>
<td>Histamine challenge</td>
<td>PD(_{15}) 0.8 vs. 1.6 mg</td>
</tr>
<tr>
<td>Northway et al., 1990</td>
<td>18</td>
<td>25 BPD</td>
<td>BW &lt;2.0 kg, Gest 33/40</td>
<td>26, no-BPD</td>
<td>Methacholine challenge; response to β(_2) agonist</td>
<td>13/25 BPD and 8/26 no-BPD had AHR; AHR unrelated to atopy</td>
</tr>
<tr>
<td>Chan et al., 1988, 1989</td>
<td>7–9</td>
<td>122 LBW</td>
<td>BW &lt;2.0 kg, Gest 32/40</td>
<td>112 term</td>
<td>Histamine challenge</td>
<td>AHR ~71% LBW vs. 43% controls, related to positive skin prick test</td>
</tr>
</tbody>
</table>

1No. S, number of subjects; No. C, number of controls; Gest, gestation; BW, birth weight.
more marked in those with a stormier neonatal course. More work is needed to determine the underlying mechanisms of AHR. The use of indirect challenge tests might enable the contribution of any cellular inflammation or neurogenic mechanisms to be determined.\textsuperscript{56} The relationship between AHR and a personal or family history of atopy, respiratory symptoms, and pre- and postnatal passive exposure to cigarette smoke remains to be determined.

**Exercise Capacity**

During exercise (see Table 5), cardiac output may increase 5-fold, as a result of increases in both heart rate and stroke volume. Minute ventilation (VE) may increase 25-fold in healthy individuals, depending on the intensity of the exercise. Carbon monoxide transfer (DL\textsubscript{co}) increases by up to 50% during exercise,\textsuperscript{57} because of recruitment and distension of the pulmonary capillaries, particularly in the upper parts of the lung. In normal subjects, ventilation-perfusion inequality decreases during exercise because of increased apical perfusion. Because cardiopulmonary limitations may not be clinically evident while the child is at rest, exercise testing may be useful in children born preterm and who developed BPD, to determine the presence and extent of any dysfunction of gas exchange secondary to alveolar growth impairment. In any exercising subject, oxygen consumption (VO\textsubscript{2}) will increase linearly with increases in workload, but will eventually reach a plateau where further increases in workload will not increase oxygen consumption. This is defined as maximum oxygen consumption (VO\textsubscript{2max}).\textsuperscript{58} VO\textsubscript{2max} is the best index for aerobic capacity, and is the gold standard for cardiorespiratory fitness.\textsuperscript{58} It is related to oxygen availability, and provides information regarding aerobic metabolism in response to exercise stress. VE also increases linearly initially but more rapidly with the production of lactic acid, since acidosis increases the ventilatory drive. VE will eventually reach a plateau with increased workload, and this is termed “maximum minute ventilation” (VEmax). Anaerobic threshold (AT) is considered an estimator of the onset of metabolic acidosis secondary to this rise in lactic acid during exercise.\textsuperscript{58} AT appears to be a good indicator of physical performance capacity, in that it correlates well with endurance capacity,\textsuperscript{59,60} and is relatively independent of maximal effort.\textsuperscript{58} Thus, important relevant markers of exercise performance include VO\textsubscript{2max}, VEmax, and AT.\textsuperscript{58} Physical training will increase both VO\textsubscript{2} and AT.

There are no longitudinal studies examining exercise performance in children who were of low birth weight and preterm. In one cross-sectional study,\textsuperscript{35} during treadmill exercise, the BPD and ex-preterm groups had increased wheezing and coughing. Although lung function did not change significantly during exercise, recovery was accompanied by a significant reduction in FEV\textsubscript{1}, in both the BPD and ex-preterm groups compared the controls. The diffusion constant (KCO), which is the mean DL\textsubscript{co} corrected for alveolar volume (VA), increased significantly above pre-exercise in the control and ex-preterm groups but not in the BPD group, suggesting problems with both or either recruitment of alveoli and distension of the alveolar capillary bed. However, effective pulmonary blood flow (Qeff) was also significantly lower in the BPD group during exercise, resulting in a low DL\textsubscript{co}. The

### Table 5—Studies of Exercise Performance After Preschool Years in Survivors of Prematurity, Low Birth Weight, and Neonatal Treatment\textsuperscript{1}

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Age (years)</th>
<th>No. S</th>
<th>BW/Gest</th>
<th>No. C</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitchell et al., 1998\textsuperscript{35}</td>
<td>6–9</td>
<td>10 BPD, 10 preterm</td>
<td>BW 1.4 kg, 31/40</td>
<td>10 term</td>
<td>Treadmill, acetylene rebreathing</td>
<td>No rise in Qeff or KCO in BPD</td>
</tr>
<tr>
<td>Jacob et al., 1997\textsuperscript{63}</td>
<td>9–13</td>
<td>15 BPD, 15 preterm</td>
<td>BW 1.1 kg, 29/40</td>
<td>13 term</td>
<td>VO\textsubscript{2max} on bicycle, CO\textsubscript{2} rebreathing</td>
<td>No difference in VO\textsubscript{2max} or Qeff, but more respiratory reserve used in BPD</td>
</tr>
<tr>
<td>Pianosi et al., 2000\textsuperscript{64}</td>
<td>8–9</td>
<td>17 BPD, 15 preterm</td>
<td>BW 1.2 kg, 28/40</td>
<td>15 term</td>
<td>Bicycle; CO\textsubscript{2} rebreathing</td>
<td>BPD, preterm had higher respiratory rates</td>
</tr>
<tr>
<td>Santuz et al., 1995\textsuperscript{65}</td>
<td>6–12</td>
<td>12 BPD</td>
<td>BW 1.4 kg, 30/40</td>
<td>16 term</td>
<td>Treadmill</td>
<td>Exercise-induced bronchospasm; higher respiratory rates; lower VO\textsubscript{2max} in BPD</td>
</tr>
<tr>
<td>Baraldi et al., 1991\textsuperscript{81}</td>
<td>7–12</td>
<td>Non-BPD, SGA = 6; AGA = 9</td>
<td>BW &lt;1.5 kg, SGA 30/40, AGA 35/40</td>
<td>26 term</td>
<td>Treadmill</td>
<td>No differences</td>
</tr>
<tr>
<td>Bader et al., 1987\textsuperscript{50}</td>
<td>9–11</td>
<td>10 BPD</td>
<td>BW 1.2 kg, 29/40</td>
<td>8 term</td>
<td>Treadmill</td>
<td>Lower VEmax, same VO\textsubscript{2max}</td>
</tr>
<tr>
<td>Kilbride et al., 2003\textsuperscript{66}</td>
<td>11</td>
<td>50 BPD and non-BPD</td>
<td>BW 0.8 kg, 26/40</td>
<td>25 term</td>
<td>Treadmill</td>
<td>Shorter exercise time</td>
</tr>
<tr>
<td>Rogers et al., 2005\textsuperscript{67}</td>
<td>53</td>
<td>BPD history not given</td>
<td>BW &lt;0.8 kg, 26/40</td>
<td>31 term</td>
<td>Step test</td>
<td>Decreased aerobic fitness</td>
</tr>
</tbody>
</table>

\textsuperscript{1}No. S, number of subjects; No. C, number of controls; Gest, gestation; BW, birth weight.
reasons for the reduced Qeff in the BPD group are not clear, and may possibly be due to right ventricular dysfunction. Although right ventricular function was not measured in this study, this was reported in BPD survivors.\textsuperscript{61,62} In contrast, two other groups showed normal cardiac responses to exercise.\textsuperscript{63,64} One group used a cycle ergometer and a respiratory mass spectrometer to measure VE and VO\textsubscript{2}max, and a steady-state test with rebreathing of a carbon dioxide (CO\textsubscript{2}) mixture to calculate Qeff. Although VO\textsubscript{2}max and absolute VEmax were not significantly different between the three groups (BPD, preterm and term), the BPD group accomplished their exercise by using a greater amount of their ventilatory reserve, determined from VEmax/maximum voluntary ventilation (MVV). Qeff was not different between groups. Pianosi et al.\textsuperscript{64} showed that cardiac output was normal with normal stroke volume and heart-rate relationships in a BPD group when compared with ex-preterm (non-BPD) and healthy term control groups, with no differences in VEmax/MVV between groups. However, they did find that the BPD and ex-preterm groups had a higher respiratory rate and maintained a lower end-tidal CO\textsubscript{2} during submaximal exercise. Santuz et al.\textsuperscript{65} used an incremental protocol on a treadmill until exhaustion and measured expired gases. They also demonstrated exercise-induced bronchospasm in their BPD group and a lower VO\textsubscript{2}max, Vemax, and ventilatory equivalent for CO\textsubscript{2} excretion (VE/VCO\textsubscript{2}) and a higher respiratory rate compared with controls, indicating both reduced aerobic capacity and ventilatory adaptation. In addition, a low AT and running time in their BPD group were observed, suggesting reduced exercise tolerance and working capacity. However, although their BPD group exercised for significantly less time than controls, these results were still evident at submaximal levels of exercise, where workloads between groups were comparable. There was no correlation between exercise performance and resting pulmonary function, duration of IPPV, and oxygen therapy. Using the same exercise protocol, Bader et al.\textsuperscript{60} observed a significantly lower VEmax with a normal VO\textsubscript{2} max in their BPD group than in the control group. A more recent study\textsuperscript{66} compared the cardiopulmonary performance of ex-preterm at rest and during exercise with that of term controls. The ex-preterm group had a shorter running time on the treadmill. Interestingly, the parents reported significantly less activity in the ex-preterm group compared with controls, so these results must be interpreted with caution, as they may merely reflect a poor level of fitness and reduced muscle mass. However, similar findings were recently observed in a group of VLBW subjects assessed at age 17 years.\textsuperscript{67} There were significant differences in motor performance in the VLBW group compared with healthy term subjects, as reflected in aerobic capacity, strength, endurance, flexibility, and activity level.

Interestingly, in the only study that assessed exercise performance in the preterm small-for-gestational-age subject (SGA) with the preterm appropriate-for-gestational-age subject (AGA), there were no significant differences between the two groups, although the sample sizes were very small.

**Summary**

Some of the conflicting data in the studies reviewed here may in part be explained by different methods of exercise testing, levels of motivation of individual subjects, different methodologies (exercise protocols and work performed), and thus different results obtained. However, these studies do suggest that for those born preterm, BPD is a risk factor for limited ventilatory reserve and/or the need for adaptation during exercise.

**LONG-TERM IMPLICATIONS OF THESE STUDIES**

For obvious reasons, there are no studies of BPD survivors into middle age. It may be that the age-related decline in respiratory function which commences in mid-adult life may be more rapid or reach a critical threshold at an earlier age in those in whom maximum fetal and early childhood growth potential was not achieved.\textsuperscript{53,52,68} There is an analogy with infant wheeze in the non-preterm. The Aberdeen group\textsuperscript{69} identified cohorts of normal, asthmatic, and “wheezy bronchitic” infants and followed them into middle age. Although no lung function measurements were made in infancy, it can be assumed on the basis of modern studies\textsuperscript{70–72} that the “wheezy bronchitics” had airflow obstruction in infancy, but normal spirometry by mid- to late childhood.\textsuperscript{73} Indeed, at age 45–50 years, this group had normal spirometry, unlike the asthmatics, who had a decrement in FEV\textsubscript{1}. However, over the preceding 12 years, FEV\textsubscript{1} had exhibited an accelerated rate of decline in the wheezy bronchitics, similar to that of the asthmatics. One could speculate that this relates to less reserve from which to decline, and a similar phenomenon will be seen in the ex-BPD who are now adults. This emphasizes the need for these survivors to be followed up into adulthood.

**IMPLICATIONS OF CHANGES IN NEONATAL PRACTICE AND FUTURE WORK**

The first pathological descriptions of BPD included an altered inflation pattern with overdistended zones alternating with atelectatic lung zones, squamous metaplasia of airway epithelium, obliterator bronchiolitis, peribronchial fibrosis, and airway smooth muscle hypertrophy.\textsuperscript{1} Impaired alveolar development was demonstrated.\textsuperscript{8,74} Pulmonary vascular histopathology included medial hypertrophy and elastin deposition in normally nonmuscularized pulmonary arterioles.\textsuperscript{1,8} These structural
changes in lung vasculature contribute to high pulmonary vascular resistance (PVR) in BPD and consequent right ventricular hypertrophy. This form of BPD is now referred to as the “old or classic BPD,” and most of the follow-up data refer to survivors of this disease. However, infants who develop the “new BPD” are more immature (typically less than 32 weeks) than those with “old BPD.” The majority of “new BPD” subjects have mild or no respiratory distress initially. They require only low or moderate concentrations of oxygen and mechanical ventilation with low pressures, and usually respond favorably to the administration of surfactant. The pathological evidence for “new BPD” in human subjects is limited. Specifically, Husain et al. looked at the mean linear intercept (MLI), which is a measure of alveolar size, in postmortem specimens of surfactant treated subjects (22 BPD and 15 non-BPD). They found that the MLI was >0.17 in BPD patients, compared to 0.12 in non-BPD controls (P < 0.01). Capillary development may also be disrupted: postmortem human specimens of preterm babies showed sparse, dilated capillaries in thinned alveolar walls. These findings were confirmed in animal models of the “new BPD.”

In summary, the pathological features of “new BPD” lungs are characterized by minimal alveolarization, sparse capillaries, less airway epithelial disease, less severe vascular disease, and less interstitial fibrosis than in “old BPD.” Thus, one of the main concerns in the “new BPD” population will be alveolar-capillary hypoplasia. It will be vital to determine whether there is catch-up growth of the lungs with age.

What are the implications for future work? First, “new” BPD (and probably in a few years, “even newer” BPD) will bring new pathophysiological problems, which must be understood and used to inform neonatal practice. Second, physiology has moved on from the days when spirometry was the high point of understanding airway function. New techniques are required, applying them longitudinally from infancy into adult life. Furthermore, we can now detect and characterize airway inflammation noninvasively, and can start to explore further the mechanisms of AHR in the survivors. Only thus can we ensure that 1) neonatal care is as “lung-protective” as possible, and 2) we understand, detect, and treat problems at an early stage in these survivors.

CONCLUSIONS

Advances in neonatal care over the last three decades have resulted in extremely preterm infants surviving, but with adverse consequences, some of which can be attributed to the very treatments that allow survival. The cardiorespiratory morbidity described above likely represents an underestimate of the true prevalence. Preterm birth is also associated with adverse neurodevelopmental outcomes (which have not been discussed here), and the majority of studies reviewed excluded those with such an outcome because of an inability to perform the tests required to establish the level of function. Since abnormal neurodevelopmental outcome can also be associated with respiratory disease, the true prevalence of respiratory morbidity in ex-preterm survivors may be difficult to establish. The residual respiratory problems of preterm LBW infants following discharge from neonatal intensive care include cough and wheeze, which may be associated with abnormal lung function, including airway obstruction and hyperinflation. There is also evidence of airway hyperresponsiveness to direct stimuli and exercise, but the pathophysiological basis for these remains to be established. There is evidence of impaired cardioventilatory performance during exercise, even in asymptomatic individuals. Some of these problems improve with age and somatic growth, but in some individuals, they are persistent. Although those who require a high level of intensive care and subsequently develop BPD are more likely to be affected beyond infancy, these adverse affects are also observed in preterm babies who did not develop initial severe respiratory distress and will therefore require ongoing surveillance.

REFERENCES