

REVIEW

Pulmonary function outcomes in bronchopulmonary dysplasia through childhood and into adulthood: implications for primary care

*Don Hayes Jr^a, J Thomas Meadows Jr^b, Brian S Murphy^c, David J Feola^d, Lori A Shook^b, Hubert O Ballard^b

^a Departments of Pediatrics and Internal Medicine, University of Kentucky College of Medicine, Kentucky Children's Hospital, Lexington, Kentucky, USA

^b Department of Pediatrics, University of Kentucky College of Medicine, Lexington, Kentucky, USA

^c Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Kentucky, USA

^d Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, Kentucky, USA

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Abstract

Bronchopulmonary dysplasia (BPD) results from prematurity and surfactant deficiency with contributing factors from barotrauma, volutrauma, and oxygen toxicity from supportive mechanical ventilation care and infection. These factors result in chronic inflammation with recurring cycles of lung damage and repair that impair alveolarisation and vascularisation in developing infant lungs. With advancement in the understanding of its pathophysiology and resulting therapy, BPD has evolved into a different disorder which has been coined the 'new' BPD. As these patients age, primary care physicians need to understand the impact on pulmonary function. This discussion reviews the pulmonary function outcomes resulting from BPD through later childhood and young adulthood.

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Introduction

Bronchopulmonary dysplasia (BPD) is the product of complex interactions between several factors that adversely affect the lungs in the neonatal period. The initial insult leading to BPD is prematurity with respiratory distress syndrome from surfactant

deficiency. Supportive care with mechanical ventilation – which can lead to barotrauma, volutrauma, and oxygen toxicity – is often a significant contributing factor. All of these factors contribute to structural lung changes that subsequently lead to effects upon lung mechanics, gas exchange, and pulmonary vasculature. The definition of BPD has evolved since Northway *et al.*¹ described lung damage resulting from mechanical ventilation

* **Corresponding author:** Dr Don Hayes Jr, Departments of Pediatrics and Internal Medicine, University of Kentucky College of Medicine, Kentucky Children's Hospital, Lexington, KY 40536, USA. Tel: +1 (859) 257-5536, Fax: +1 (859) 257-1888 E-mail: don.hayes@uky.edu

Table 1. Diagnostic criteria for BPD.†

	Gestational age	
	<32 weeks	≥32 weeks
Time point of assessment	36 weeks PMA or discharge to home, whichever comes first Treatment with oxygen >21% for at least 28 days <i>plus</i>	>28 days but <56 days postnatal age or discharge to home, whichever comes first
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need* for <30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need* for <30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need* for ≥30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need* for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge, whichever comes first

BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = postmenstrual age; PPV = positive-pressure ventilation.

*A physiological test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnoea, retractions, rales) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen >21% and/or positive pressure for non-respiratory disease (e.g. central apnoea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen >21% means that the infant received oxygen >21% for more than 12 hrs on that day. Treatment with oxygen >21% and/or positive pressure at 36 weeks PMA or at 56 days postnatal age or discharge should not reflect an "acute" event but should rather reflect the infant's usual daily therapy for several days preceding and following 36 weeks PMA, 56 days postnatal age or discharge.

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in premature infants with severe respiratory distress syndrome. The National Institutes of Child Health and Human Development (NICHD) workshop established the diagnostic criteria for BPD based on gestational age and disease severity as illustrated in Table 1.² Ehrenkranz *et al.*³ validated the accuracy of the consensus definition of BPD in early infancy compared to other diagnostic definitions.³

The pathological findings of 'classic' BPD or hyaline membrane disease were classified histologically into four groups:⁴ acute lung injury, proliferative phase, early repair phase, and late repair phase. Advances in the treatment of preterm infants with lung disease have changed the prognosis and long-term survival of this patient population. The impact of surfactant therapy on the pathophysiology of BPD and alveolar developmental arrest was well defined by Husain *et al.*⁵ The findings of arrested alveolar development contradict the theory that BPD improves as a child ages due to continued lung development during the alveolar stage of lung development that continues after birth. In the post-surfactant era, histological changes in BPD include fewer and larger simplified alveoli, negligible airway lesions, variable airway smooth muscle hyperplasia, variable interstitial fibroproliferation, fewer and dysmorphic capillaries, and less severe arterial lesions, so the term new 'BPD' has been coined.⁵ The distal lung acinus, which has large alveoli with reduced secondary crest formation, is a primary finding in the 'new' BPD.⁵

The evolution of histological changes of 'classic' BPD to 'new' BPD was nicely reviewed by Coalson.⁶ As BPD undergoes changes due to evolving new therapy in the neonatal period, there will be a direct impact upon clinical outcomes – especially from a pulmonary aspect – later in the life of these patients. An understanding of these evolutionary changes of BPD and the pulmonary function outcomes are important for primary care physicians. This review encompasses a discussion of pulmonary function outcomes of BPD through childhood into adulthood according to the current medical literature.

Pulmonary function outcomes

Early and middle childhood

Early pulmonary complications are present in BPD, with several studies identifying abnormalities continuing to exist throughout childhood.

Respiratory mechanics, including resistance and compliance, are impaired during the early phases of BPD but subsequently improve, most likely due to airway growth and development of new alveoli. Several studies have demonstrated improvement in lung function during early childhood. Using passive respiratory system compliance and resistance during mechanical ventilation, Baraldi *et al.*⁷ measured pulmonary mechanics and functional residual capacity (FRC) as well as forced expiratory flow in infants weighing less than 1250g who were BPD survivors until 2 years

of age. There was improvement in lung function during the first years of life, reaching a normal value range by 2 years of age, but substantial impairment of airway function – as measured by reduced forced expiratory flows – continued.⁷

Chronic airway obstruction typically persists in former premature infants with 'classic' BPD during early childhood.⁸⁻¹¹ The airway obstruction is typically fixed, meaning that it is unresponsive to β_2 -agonists.¹¹ The mechanism of development of fixed airway obstruction is most likely related to early life structural changes in the airways. Blayney *et al.*¹² demonstrated that patients with 'classic' BPD who had normal pulmonary function at age 7 years had normal lung growth and that those with mild to moderate lung disease continued to have lung growth and/or repair during their school years in a cohort of 32 BPD survivors at age 7 and 10 years. Furthermore, the cohort at ages 7 and 10 years maintained normal mean total lung capacity (TLC) and FRC with elevation of mean residual volume (RV) and the RV/TLC ratios.¹² At the age of 7 years, 19/32 patients (59%) who had a forced expiratory volume in 1s (FEV₁) <80% had improvement by 10 years of age (from 65±11% to 72±16% of the predicted value).¹² The majority of patients had a positive methacholine challenge test result at both ages, although there was a low incidence of clinically diagnosed asthma.¹²

In another study involving infants with 'classic' BPD, lung volume increased normally, reportedly due to formation of new alveoli leading to improvement in lung compliance.¹³ In this cohort of infants, airway growth was slow during the first 6 months after birth with subsequent faster growth, leading to normalisation of conductance values by 3 years of age.¹³ Pulmonary function testing using pneumotachography, oesophageal pressure monitoring with a water-filled feeding tube, and a modified nitrogen washout technique, was performed to assess FRC in 39 infants (mean gestational age at birth 29.8 weeks, mean birth weight 1140g) with BPD who required mechanical ventilation during the first weeks of life for a median of 9 days and supplemental oxygen for a median of 48 days.¹³ The FRC decreased during the first 6 months after birth but thereafter returned to the normal range.¹³ Lung compliance improved from 50% to 80% of normal at 1 and 36 months, respectively.¹³ Pulmonary conductance was 50% of normal at 1 month, increased little during the first 6 months, but improved to 85% of normal at 3 years of age.¹³ More recently, using the raised volume rapid thoracoabdominal compression technique and whole-body plethysmography, Robin *et al.*¹⁴ showed that infants with 'new' BPD have pulmonary function abnormalities characterised as mild to moderate airflow obstruction with air trapping.¹⁴ The study involved 28 children with a history of prematurity; mean gestational age at birth was 26.4 weeks and mean birth weight was 898g, with a mean chronological age at pulmonary function testing of 17 months.¹⁴ Compared to a previously studied group of healthy infants, the children with

BPD had decreased forced expiratory flows – including forced expiratory volume in 0.5s (FEV_{0.5}), forced expiratory flow at 75% of expired forced vital capacity (FEF_{75%}), and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75%}) – in addition to increased FRC, RV, and RV/TLC ratio, with no difference in TLC between the two groups.¹⁴ Infants with recurrent wheezing showed greater expiratory flow limitation, airways responsiveness, and hyperinflation, whereas infants without wheezing had only modest airway dysfunction.¹⁴

Preterm children with a history of BPD more commonly have abnormal pulmonary function along with bronchodilator responsiveness as compared to preterm children without BPD and children born term.¹⁵ Airway obstruction was more prevalent with a significant reduction in mean forced vital capacity (FVC), FEV₁, and FEF_{25-75%} – along with bronchodilator responsiveness occurring twice as often in preterm children with a history of BPD than in preterm children without a history of BPD – in a study evaluating 7-year-old survivors.¹⁵ Pulmonary function in the preterm children without a history of BPD was similar to that of the term control group.¹⁵ Persistent airway obstruction was previously described by Smyth *et al.*¹⁶ in nine children with BPD at a mean age of 8.4 years, with six of eight children having positive methacholine challenge tests, thus indicating bronchial hyperreactivity. Children born with very low birth weight (VLBW) who developed BPD had lower lung function at 11 years of age compared to other surviving VLBW children who did not develop BPD, although this difference did not reach clinical significance.¹⁷ Furthermore, there was no significant difference in lung function between children who required ventilation at birth and did not develop BPD and children not requiring assisted ventilation.¹⁷

Several studies have evaluated the physiological response to exercise in late childhood of children with a history of BPD. Bader *et al.* assessed pulmonary function testing and graded exercise stress testing in 10 children of mean age 10.4 years who were survivors of BPD compared to eight age-matched normal children born at term.¹⁸ Airway obstruction, hyperinflation, and airway hyperreactivity with RV, RV/TLC ratio, FVC, FEV₁, FEF_{25-75%}, and maximal expiratory flows at 80%, 70%, and 60% of TLC were all abnormal in children with a history of BPD compared to the controls.¹⁸ Aerobic fitness was not significantly different between the BPD and control groups, but was achieved in the BPD group at the expense of a reduction in arterial oxygen saturation (SaO₂) and a rise in transcutaneous CO₂ tension (tcPCO₂).¹⁸ Pre-exercise tcPCO₂ was higher in the BPD group than in the control group.¹⁸ At maximal workload, tcPCO₂ remained high in patients with BPD compared to the control group and SaO₂ fell below pre-exercise levels in the BPD group but not in the control group.¹⁸ Exercise-induced bronchospasm occurred in 50% of the BPD group and did not occur in the control group.¹⁸ Moreover, long-term airway obstruction and mild exercise intolerance was reported in premature infants with

BPD later in childhood, with a milder degree of airway obstruction in premature infants who did not have BPD.¹⁹

In late childhood, pulmonary function and exercise tolerance were evaluated in two groups: group 1 comprised children with a history of BPD (mean gestational age 29.6 weeks, mean birth weight 1367g, mean testing age 7.9 years); and group 2 comprised children with no history of BPD (mean gestational age 30.3 weeks, mean birth weight 1440g, mean testing age 7.8 years) with a control group (term gestation, similar age and height at time of testing).¹⁹ Total lung resistance was significantly higher and dynamic lung compliance was decreased in group 1 (positive history of BPD) compared to group 2 and the control group.¹⁹ FEV₁ and FEV₁/FVC were lower in group 1 than in group 2 and the control group.¹⁹ Additionally, exercise testing performed in six boys with BPD showed that the ratio between minute ventilation (VE) at maximal workload (VE_{max}) and the predicted value of maximal voluntary ventilation was increased compared to five boys from both group 2 and the control group.¹⁹

Using stepwise exercise on a treadmill, maximum oxygen consumption (VO₂) and VE were significantly lower in children aged 6 to 12 years (mean gestational age 30 weeks, mean birth weight 1400g) who had a history of BPD compared to a healthy control group. Additionally, submaximal levels of exercise dynamic, VO₂, and VE responses were significantly lower in the BPD group with a ventilatory pattern characterised by lower tidal volumes.²⁰ In addition to ventilation defects, there are reports of diffusion abnormalities due to persistent structural changes in lung tissues and airways. The diffusing capacity of the lung for carbon monoxide (DLCO) measured using the single breath method was significantly lower in two groups of premature children with birth weights <1250g – one group with BPD and the other without – than in a control group of children born at term.²¹

A reduction in the alveolar surface area in survivors with BPD likely limits gas transfer both at rest and during exercise.²² In a three-phase protocol, intrabreath acetylene (C₂H₂) and carbon monoxide (CO) transfer, pulmonary function, and SaO₂ during treadmill exercise testing were measured in 10 survivors with BPD, 10 children born prematurely without BPD, and 10 healthy children born at term between the ages of 6 and 9 years.²² At rest and during exercise, C₂H₂ transfer corrected for body surface area was lower in survivors with BPD than in children born prematurely without BPD and children born at term.²² With exercise, the transfer of both gases increased sharply over resting values in premature children without BPD and in those born at term; however, in survivors with BPD, C₂H₂ transfer with exercise increased – but not to the extent of that in the control subjects – and corrected CO transfer did not change.²² In premature children with BPD and premature children without BPD, the FEV₁ fell during recovery from exercise, but this did not correlate with

C₂H₂ transfer or diffusing capacity corrected for alveolar volume (DLCO/VA).²² Soluble gas transfer at rest and during acute exercise was reduced in children who survived BPD. This can be explained either by long-term disruption of lung structure or residual right ventricular dysfunction affecting cardiac output.²²

Adolescence and adulthood

As BPD survivors are now reaching the adult years, few studies have assessed their pulmonary function. Those individuals who have participated in studies continue to show different degrees of pulmonary function changes, primarily due to airway obstruction. In 1990, Northway and colleagues assessed the pulmonary function of 26 adolescents and young adults born between 1964 and 1973 who had BPD during infancy compared to two control groups (26 age-matched adolescents and young adults of similar birth weight and gestational age who had not undergone mechanical ventilation and 53 age-matched normal subjects).²³ Sixty-eight percent of the subjects with a history of BPD in infancy (17 of the 25 tested) had airway obstruction, including decreases in FEV₁, FEF_{25-75%}, and maximal expiratory flow velocity at 50% of vital capacity compared to both control groups.²³ Twenty-four percent of the subjects with a history of BPD during infancy had fixed airway obstruction and 52% had reactive airway disease, defined by response to the administration of methacholine or a bronchodilator.²³ Hyperinflation, determined by an increase in the RV/TLC ratio, was more frequent in the subjects with a history of BPD than in either the matched cohort or the normal controls.²³ Six of the subjects who had BPD during infancy had severe pulmonary dysfunction or current symptoms of respiratory difficulty.²³ More recently, the relationship between lung function in late adolescence and BPD was determined by the assessment of lung function tests at a mean age of 18.9 years in 147 survivors with birth weight <1500g born from 1977 to 1982.²⁴ A total of 33 of the 147 subjects (22%) had BPD during the newborn period.²⁴ All of the lung function variables reflecting airflow were substantially diminished in the group with BPD without significant differences in lung volumes, and more subjects in the BPD group had airflow reduction in the clinically significant range including FEV₁/FVC ratio <75%.²⁴ Compared to measurements earlier in childhood, the FEV₁/FVC ratio deteriorated more in subjects with BPD between 8 and 18 years, therefore, adolescents with a history of VLBW and BPD in the newborn period have pulmonary function that is deteriorating at a more rapid rate.²⁴

In a prospective cohort study, airway obstruction and a lower DLCO was demonstrated in children born with a gestational age of <32 weeks and/or birth weight <1500g in a group of patients followed for up to 19 years compared to healthy term control subjects.²⁵ In addition to lower FEV₁ and reduced DLCO, preterm birth was associated with reduced exercise capacity compared to

Table 2. Pulmonary function abnormalities due to BPD in later childhood and adulthood.

	First authors	Citation
Airway obstruction	Bader, Parat, Vrijlandt	18, 19, 25
Fixed	Northway	23
Reversible		
Responsive to β_2 -agonist	Northway	23
Responsive to methacholine	Northway	23
Increased total lung resistance	Parat	19
Reduction of pulmonary function variables	Doyle	24
Forced expiratory volume in 1 s	Parat, Northway, Vrijlandt, Halvorsen	19, 23, 25, 26
Forced expiratory flow at 25–75% of vital capacity	Northway	23
Maximal expiratory flow velocity	Northway	23
Diffusion capacity	Hakulinen, Mitchell, Vrijlandt	21, 22, 25
Elevation of pulmonary function variables		
Residual volume	Northway	23
Residual volume to total lung capacity ratio	Northway	23

control subjects, which could not be explained by impaired pulmonary function or smoking habits but may be related to impaired physical fitness.²⁵ A substantial decrease in FEV₁, an increase in bronchial hyperresponsiveness, and a number of established risk factors for steeper age-related decline in pulmonary function of patients born prematurely (gestational age ≤ 28 weeks or birth weight ≤ 1000 g) was identified at a mean age of 17.7 years.²⁶ The diagnosis of asthma by a physician and use of asthma inhalers were significantly more prevalent among patients born prematurely than controls.²⁶

Table 2 summarises the pulmonary function abnormalities in patients with BPD in later childhood and young adulthood as discussed in the last two sections.

Pulmonary function and emphysema in adult survivors of BPD

In 21 adults (median age 19 years, range 17–33) who were survivors of moderate and severe BPD during infancy, computed tomographic (CT) imaging of the chest demonstrated abnormal findings, with emphysema being the most common (84%).²⁷ The extent of emphysema on the CT scans was inversely related to the FEV₁ z-score.²⁷

Conclusions

BPD requires intensive care during the neonatal period and close follow-up during infancy. Typically, these patients develop long-term pulmonary complications as a result of structural changes in the airways and lung that persist into adulthood. These complications include chronic pulmonary function impairment, reduced exercise capacity, and more rapid deterioration of lung function than in normal subjects as adolescents and young adults. In general, the reduction in exercise capacity results from a reduction in ventilatory reserve. Owing to the advances in therapy and management, BPD is an evolving disease. This is an

important issue for primary care physicians who will be involved with the care of these patients. The ‘new’ BPD in the post-surfactant era has different pathophysiological changes and different radiological and clinical presentations compared to ‘classic’ BPD. These changes should also influence pulmonary function later in childhood and adulthood, with speculation that there will be less impairment or possibly improvement. However, further longitudinal studies are needed to investigate the long-term pulmonary function outcomes of BPD in the post-surfactant era. As the pathophysiology of BPD evolves as treatment improves, the delivery of primary care for these patients later in life will also be transformed as there will be a direct impact upon pulmonary function later in childhood and ultimately in adulthood.

Conflict of interests

The authors have no commercial or proprietary interest in any drug, device, or equipment mentioned in this manuscript.

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COMMENTARY

Bronchopulmonary dysplasia: the challenges for primary care

*Duncan Keeley^{a,b}

^a General Practitioner, Thame, Oxfordshire, OX9 3JZ, UK

^b Policy Lead, PCRS-UK Executive

Over the last 40 years there has been enormous progress in the care of children born prematurely. The first systematic description of bronchopulmonary dysplasia (BPD) – a syndrome of chronic lung damage in premature babies receiving mechanical ventilation and high concentrations of oxygen – was published in 1967; the mean gestation was 34 weeks, the mean birthweight 2.2kg, and the mortality was 67%. Improvements in neonatal care, including better methods of ventilation and the use of

exogenous surfactant in the treatment of hyaline membrane disease, have resulted in the survival of infants of progressively lower birthweight so that now the majority of infants affected by BPD were born weighing less than 1kg.¹ The pattern of pathological changes has evolved, with fewer changes in airway epithelium and less fibroproliferative change, but prominent impairment of alveolar and vascular development. This “new” pattern of BPD may occur in infants who have needed relatively

* Corresponding author: Dr Duncan Keeley, The Health Centre, East Street, Thame, Oxon, OX9 3JZ, UK

Tel: +44 (0)1844 261066 Fax +44 (0)1844 260347 E-mail: auby17@dsl.pipex.com

little ventilatory support.² Infants with BPD may have protracted oxygen dependence. Diffuse abnormality of chest radiographs is common but correlates poorly with the degree of lung function abnormality.

This review article by Hayes *et al.*³ summarises the evidence of continuing abnormalities in lung function affecting infants with BPD surviving into childhood and adulthood. At all ages studied, lung function abnormalities – including reductions in FEV₁ and expiratory flow, and increased rates of bronchial hyperreactivity and airway obstruction – were more prevalent in children and young adults who had had BPD than in children born at term or children born prematurely who had not developed BPD.

What are the implications of these findings for clinicians in primary care? Children discharged from premature baby units who remain oxygen dependent usually receive continued supervision in the community from specialist community paediatric nursing services together with easy access to hospital paediatric teams, but primary care clinicians need to be fully aware of the situation and involved in sharing care. The practicalities of caring for a premature infant both before and after discharge from hospital can put enormous strain on parents and siblings, and their health and emotional needs must be remembered.

Knowledge of the child when well facilitates clinical assessment of intercurrent illness. Clinical deterioration may occur in the context of acute infections or due to the development of reactive airway disease or pulmonary hypertension. Infants with BPD are at high risk of re-admission to hospital with respiratory complications in the first two years of life, especially in the context of RSV infection. The prophylactic use of monoclonal antibody to RSV (palivizumab) has been advocated, and may be cost-effective.⁴ Thresholds for face-to-face clinical assessment of respiratory illness – including pulse oximetry – and for hospital admission need to be lower in children with BPD.

In addition, it is important that primary care clinical record summaries should include important perinatal details, including the weight and gestation at birth of infants born prematurely. A diagnosis of BPD should be separately recorded. Completion of routine immunisations is important.

In later childhood and adult life primary care clinicians should be aware of the perinatal history and of the increased likelihood of respiratory disorders. Spirometry with reversibility testing

should be performed in those with overt recurrent respiratory symptoms,⁵ and referral should be considered if there has been no recent specialist respiratory assessment. Influenza immunisation should be offered. If asthma is diagnosed it should be managed according to recognised guidelines. Avoidance of tobacco smoking is very important, and every effort should be made to achieve smoking cessation in patients with a history of BPD who do smoke.

It is recognised that assessment of the effects of management practices in the neonatal respiratory care of premature infants should preferably include determination of clinical and physiological outcomes in the medium to long term, but there are no comprehensive follow-up studies into adult life. In an earlier review, Kinsella and colleagues argued that, “More research is needed to determine the long-term respiratory course of premature neonates, with or without severe BPD, and their relative contribution to the growing adult population with chronic obstructive pulmonary disease.”¹ Better recording of basic neonatal histories in primary care would help facilitate such enquiries as well as improving the care of individuals.

Conflict of interests

None.

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