

Clinical Pulmonary Function Testing for Children with Bronchopulmonary Dysplasia

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Many more extremely preterm children are now surviving, many of whom develop bronchopulmonary dysplasia (BPD), most commonly defined as continuing supplemental oxygen requirements beyond 36 weeks postmenstrual age. Respiratory symptoms usually diminish with increasing lung growth and development, such that it may be assumed that the child has “outgrown” their breathing problems, with follow-up focusing on neurological problems. However, deficits in lung function may persist into school age and beyond, and such individuals are at increased risk of life-long respiratory problems. Although numerous research studies have utilized pulmonary function tests (PFTs) to investigate respiratory problems from infancy through to adulthood, these tests are less frequently used in the clinical management of individual children. With the exception of the hypoxic fitness-to-fly test, PFTs do not yet have a defined role in clinical management of infants surviving BPD and their applications in preschool children may be limited by the reduced concentration and coordination associated with extremely preterm birth. There is, however, a potentially important role for objective assessments using PFTs in school-age children and adolescents to determine whether there is coexistence of true asthma and exercise-induced bronchoconstriction or bronchomalacia, to evaluate exercise capacity and, in severe cases, to investigate the development of pulmonary hypertension. BPD-associated adult lung disease is likely to be seen with increased frequency as these individuals age.

Introduction

OVER THE PAST 3 decades, advances in prenatal and neonatal intensive care have contributed to marked improvements in survival rates for extremely preterm infants.^{1–5} However, the prevalence of pulmonary sequelae in such infants has not declined.^{6–8} This, combined with an overall increase in the incidence of spontaneous live preterm births,⁹ means that the respiratory burden of preterm birth (including that relating to late preterm births¹⁰), is increasing in clinical, financial, and social terms.^{11–13} Despite the increased respiratory morbidity in survivors of bronchopulmonary dysplasia (BPD), clinical follow-up beyond infancy tends to concentrate on neurological outcomes and rarely includes objective assessments of pulmonary function. As discussed below, this may reflect a lack of awareness of the increased risk of developing chronic obstructive pulmonary disease (COPD) in later life that such individuals face.^{14,15}

The original description of BPD¹⁶ is of a syndrome now rarely encountered. The histopathological lesions of severe airway injury and alternating sites of overinflation and fibrosis in “old BPD” have been replaced in “new BPD” by pathologic changes of large, simplified alveolar structures, a

dysmorphic capillary configuration, and variable interstitial cellularity and/or fibroproliferation.^{11,17–20} Airway and vascular lesions tend to be restricted to those infants who develop more severe disease. The original concept that “new BPD” results in arrested alveolarization has now been modified to that of impaired alveolarization, because continued alveolar formation can occur with the gentler ventilatory support now commonly used.^{19,21} This change in pathology means that follow-up studies of current adult survivors of preterm birth and “old BPD” may not be entirely relevant to those now treated with modern obstetric and neonatal care.

The pathogenesis underlying the airflow obstruction, heightened airway responsiveness, and increased susceptibility to wheezing illnesses seen in survivors of BPD irrespective of the era in which they were born^{7,11,22–27} remains poorly understood. However, animal models suggest that hyperoxic insults to the immature lung may not only result in epithelial and smooth muscle hyperplasia and airway remodeling^{28,29} but also reprogram key innate immunoregulatory pathways in the lung,³⁰ thereby contributing to both reduced resistance to respiratory viral infections and long-term risk of COPD. Morphological studies in infants who died with “old BPD” have reported substantial thickening of

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airway wall dimensions over the entire size range of airways when compared with infants who succumbed to sudden infant death syndrome, which would be associated with airflow obstruction in survivors.³¹

The risk of developing BPD (commonly defined as those continuing to require supplementary oxygen beyond 36 weeks postmenstrual age, though numerous alternative definitions have been used,^{32–35} is increased in those who are born extremely preterm (<28 weeks gestation), have evidence of pre- or postnatal inflammation,^{28,36–38} are male,³⁹ or are genetically susceptible.^{40–42} BPD develops as the net result of pulmonary inflammation, oxidant stress, mechanical trauma to these extremely fragile and immature lungs, respiratory infections, and disruption of normal alveolar and vascular development.¹⁹ It has been suggested that the incidence of BPD may be reduced by introducing early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery,⁴³ but such findings have yet to be confirmed in prospective cohort studies. The importance of minimizing iatrogenic damage to the developing lung due to intubation, positive pressure ventilation, hyperoxic gas mixtures, or excessive use of systemic steroids has been emphasized in recent studies, with increasing evidence that such exposures should be avoided where possible or minimized if they are required to sustain life.^{44–46} BPD is part of a much wider spectrum of lung disease that may persist after preterm birth, even in the absence of neonatal respiratory problems.^{47–50}

The potential impact of extremely preterm delivery on subsequent respiratory health requires an appreciation of early lung development.^{51,52} All the pre-acinar (conducting) airways are formed during the first trimester of pregnancy, whereas development of an efficient blood-gas barrier for pulmonary gas exchange occurs much later.⁵³ Although it is generally agreed that lung growth is primarily by alveolar multiplication during early childhood with subsequent growth being attributed to increase in alveolar dimensions,^{21,53,54} until recently there has been no direct technique to study airspace development. New noninvasive methods using the diffusion properties of stable noble gas isotopes such as hyperpolarized Helium, which can be detected using magnetic resonance,⁵⁵ could provide a sensitive window on the acinus to further clarify the impact of pre- and early postnatal insults to the developing lung. There is considerable evidence that factors disrupting lung development^{37,56} may have life-long effects^{14,15} and that lung function “tracks” throughout life, those with the lowest lung function during infancy and early childhood retaining this position thereafter.^{11,57,58}

Although respiratory symptoms and rehospitalizations are common in the first few years of life in those who develop BPD, these tend to diminish with increasing lung and airway growth and development, such that parents and clinicians may assume that the child has “grown out” of their respiratory problems. However, deficits in lung function persist into school age and beyond, and such individuals may be at increased risk of life-long respiratory problems.^{11,57–73} The normal age-related decline in lung function from the mid twenties onward⁷⁴ is of little practical consequence in healthy subjects because of the availability of considerable lung reserves. There is, however, increasing evidence that COPD, which is set to become the third most

important cause of death globally,⁷⁵ is not simply confined to those who experience an accelerated decline in lung function with aging, but may also occur in those who fail to reach their full potential as young adults because of insults to the developing lung, including those with prior BPD.^{14,15}

This review summarizes the extent to which pulmonary function tests (PFTs) have been used in clinical research and indicates the extent to which they may or may not be useful at different ages in the clinical management of survivors of BPD.

Measuring Lung Function Through Infancy and Childhood

Infants

There have been many clinical research studies using infant PFTs to assess both the impact of BPD and also less severe forms of chronic neonatal lung disease during the first 2 years of life, as summarized in a recent review series.^{76–82} Although infant PFTs could potentially provide valuable, objective evidence regarding an individual's response to inhaled steroids or bronchodilators, the current paucity of appropriate normative data⁸³ and information on within-subject changes over specified time periods⁸⁴ limits the confidence with which such measurements can be interpreted. In addition, infant PFTs are generally limited to specialized research centers and require sedation, which limits how frequently they can be repeated.⁸⁵ As the clinical usefulness of PFTs in infants recovering from BPD has yet to be established (see Role of Lung Function Tests When Monitoring Children with Prior BPD section), use of such tests in this age range will be discussed only briefly.

The common tests applied in infants with BPD are as follows:

- Neonatal intensive care unit: Measurements in intubated infants and those receiving ventilatory support are generally based on assessments of respiratory mechanics (occlusion techniques), airway function (forced deflation technique), lung volumes and ventilation inhomogeneity using multiple breath, washout techniques, and breathing patterns (respiratory inductance plethysmography).⁸⁶ The majority of these tests are currently used as outcome measures in clinical research rather than playing any role in routine clinical management.
- Neonatal unit: Once a baby has been extubated and is breathing spontaneously, most PFTs are undertaken without sedation (up to at least 44 weeks postconceptional age) and include tidal volume measurements and expiratory flow ratios,⁸⁷ functional residual capacity,⁸⁰ ventilation inhomogeneity by gas dilution or washout techniques,^{22,82,87–90} and assessments of passive respiratory mechanics using the occlusion techniques.^{79,91}
- Subsequent follow-up during infancy generally requires sedation and is focused on airway function using the tidal or raised volume techniques,^{81,92–94} although body plethysmography has also been used to assess gas trapping secondary to airway obstruction.^{80,95,96} Most measures of lung volumes only reflect overall lung size, without any indication of the surface area available for gas exchange, a limitation recently overcome by applying a novel adaptation of the carbon monoxide diffusion technique in both

healthy infants and those recovering from BPD.⁹⁷ The potential impact of different patterns of somatic growth in children born preterm also needs to be considered when interpreting either baseline measures of lung function⁸⁹ or longitudinal changes during infancy.⁹⁸

In summary, during the early stages of BPD, lung function is characterized by

- reduced lung volume and compliance;
- reduced airway caliber, manifested by increased resistance, and reduced forced expiratory flows and volumes; and
- altered gas mixing efficiency and reduced pulmonary diffusing capacity.

The relatively normal lung clearance index reported in infants with chronic lung disease by term equivalent^{87,89} suggests that any airway obstruction may be relatively homogenous at this stage. An elevated lung clearance index has been reported in school-age children with prior BPD⁶¹ (see School Children and Adolescents with BPD section), which may reflect airway remodeling subsequent to lung injury during the neonatal period.

Oxygenation usually normalizes during the first year of life, but there may be persistent airflow obstruction, which may worsen in the first year of life.^{50,99,100} Diminished airway function has also been reported throughout the first year in infants born preterm requiring no ventilatory support.^{48,49,89}

Toddlers/preschoolers

Although it is now possible to undertake a wide range of PFTs in both healthy preschool children (ie, 3–6 years of age) and those with respiratory diseases such as asthma or cystic fibrosis,^{85,101} application of these tests in very young children with prior BPD has often been limited by neurodevelopmental morbidity.¹⁰² Thus, with the exception of a few clinical research studies that have used simple, noninvasive tests such as Interrupter Resistance or the Forced Oscillation Technique,^{73,101,103,104} results of which are summarized in Table 1, there is limited evidence of the feasibility and usefulness of such tests in the clinical management of individual children with BPD before 5–6 years of age.

School children and adolescents with BPD

A wide selection of PFTs and exercise tests has been used to assess cardiopulmonary function in school-age children born preterm with or without BPD. These range from the widespread use of spirometry, which has been the major outcome variable in most of the larger birth cohort studies^{59,60,105,106} and which, with appropriate training, is applicable outside specialized lung function laboratories,¹⁰⁷ to more complex assessments of airway reactivity, ventilation distribution, pulmonary blood flow, and exercise capacity. Details of studies that have been undertaken to investigate the long-term effects of BPD on respiratory function are summarized in Table 1. Although there is considerable evidence that lung function continues to be diminished in children with BPD throughout the school years,^{6,11,25,60,61,92,105,106,108–115} interpretation of the nature and severity of such changes may be dependent on the availability of a contemporary control group,¹¹⁶ which was

lacking in many of the earlier studies (Table 1). The normal age-related decline in the ratio of forced expired volume in 1 s (FEV₁) to forced vital capacity (FVC)⁷⁴ is accelerated in children and adolescents with prior BPD,¹⁰⁵ especially in those who take up smoking.¹¹⁷

Knowledge regarding respiratory morbidity and persistent functional deficits during adolescence and adulthood in those with prior “old” BPD is relatively limited because of low survival of such individuals prior to 1970.¹¹⁸ Although respiratory symptoms such as cough, wheeze, and frequent need for medication do decline as the child grows toward adulthood, their prevalence remains considerably higher than in the general population.¹¹⁹ In addition, the prevalence of respiratory symptoms has been shown to be lower than that of lung function abnormalities,^{11,24,60,61,112,113} suggesting that long-term impact of BPD will be underestimated if based purely on symptoms. Factors other than diminished lung function, such as alterations in immune response and control of breathing, may also contribute to the clinical manifestations of respiratory disease. With the exception of one study of relatively mature infants,¹²⁰ persistent reductions in spirometric lung function by, on average, around 20% have been reported in survivors of BPD and preterm birth, when compared with full-term peers.^{59,121,122} Despite the marked changes in obstetric and neonatal care, the magnitude of such changes during childhood and adolescence appears to have remained constant over the past 30 years,¹¹ albeit the populations studied have become increasingly preterm.

In summary, the main functional changes observed in school children and adolescents with prior BPD include:

- Airway obstruction (decreased FVC, FEV₁, FEV₁/FVC, forced expiratory flow between 25% and 75% of FVC, peak expired flows, and increased airway resistance)
- Gas trapping (increased residual volume and ratio of residual volume/total lung capacity)
- Reductions in gas mixing efficiency (increased lung clearance index)
- Diminished pulmonary blood flow in some, but not all, studies
- Decreased oxygen consumption during maximal exercise
- Diminished exercise capacity or altered response to exercise, including changes in pulmonary blood flow during exercise
- Increased bronchial hyperresponsiveness and response to bronchodilators.

Despite these decrements in lung function and the increased bronchial reactivity and prevalence of wheeze and doctor-diagnosed “asthma” reported in so many studies, there is no increase in atopy or evidence of eosinophilic inflammation (no elevation of exhaled nitric oxide levels) in these children, suggesting that the underlying pathophysiology for wheeze is not that seen in “typical” childhood asthma, and may have a structural rather than inflammatory basis.^{61,108} This underscores the need to try to document the extent to which airflow obstruction varies over time and with treatment before making a diagnosis of asthma. An improved understanding of the wheezing phenotype presented by these children is also essential if appropriate anti-inflammatory treatment is to be provided at an early stage to treat symptoms in those who will benefit, while avoiding overtreatment, with potentially harmful side effects, in others.^{123,124}

TABLE 1. SUMMARY OF LUNG FUNCTION STUDIES IN CHILDREN WITH BRONCHOPULMONARY DYSPLASIA AND AGED > 3 YEARS

Author's details	Birth year	n (% BPD)	Controls n	GA (w)	Test age (year)	PFT outcomes	CPET	Comments/findings
Northway ¹¹⁸ United States	1964–1973	25 (100% BPD)	26 PTC 53 FTC	33 (3.8) 35 (3.6) ~40	18.3 (2.7) 18.8 (2.7) 18.0 (3.1)	FRC _N ; DL _{CO} FRC _{pleth} ; Raw; FEFV; BDR; BHR (MCh)	N	AO in 68% with prior BPD (of whom 24% fixed AO and 52% reactive AO). RV/TLC and FRC +ve association with duration and intensity of neonatal ventilatory support.
Chan ^{66,67} United Kingdom	1979–1980	122 and 130 (8% BPD)	112 and 120	32 [27–39]	7.0 (0.2) 7.0 (0.4)	BHR (hist.); ST (LBW group only); FEFV	N	↓ LF associated with LBW, male sex, and maternal smoking. ↓ LF in LBW associated with cough but not wheeze. +ve ST significantly associated with BHR in LBW group.
Narang ^{62,120} United Kingdom	1979–1980	60 LBW (12% BPD)	50	32 [27–37] 40 [36–43]	22 (20–23) 23 (19–25)	FEFV; BHR (MCh)	Y	↑ Respiratory symptoms in LBW cf. controls, but no significant difference in LF, BHR, or exercise capacity between groups.
Doyle ^{105,106,110} Australia	1977–1982 1980–1982	67–78 VLBW (42% BPD) 154 VLBW: 10% BPD 41 no BPD 98 no IPPV		27.5 (2.3) 27 (1.5)	8, 14, and 19 years	FEFV; FRC _{pleth}	N	Combination of SGA + LBW: poorer outcomes. Serial measurements in 2 cohorts reported at different ages and combinations. Conclusions vary slightly according to subsets. Although most BPD children had LF within “normal range,” LF significantly ↓ in those with BPD versus those without at all ages.
Anand ⁶⁴ United Kingdom	1980–1981	128 VLBW	37–42 FTC at 14 and 18 years	29 (1.4) 30 (1.8) 40.0	8, 11, and 14 years			By 19 years, LF in no BPD VLBW survivors within “normal range,” although ↓ compared with FTC. Significantly ↓ LF and ↑ AO in BPD survivors. More rapid age-related decline in LF in BPD than FTC.
Kennedy ¹¹³ Australia	1981–1982	102 VLBW (25% BPD)	128 FTC	30.7 (2.7) > 37	15.0	FEFV	N	Evidence of persistent AO in VLBW adolescents, effect associated with GA rather than IUGR. VLBW also more prone to chronic cough, wheeze, and asthma.
Halvorsen ²⁴ Norway	1982–1985 1991–1992	81 PT (77% BPD)	82 FTC	29.6 (2.8) > 37.0	11.3 (0.8) 11.4 (0.8)	FEFV; FRC _{pleth}	N	Marked ↓ in LF in BPD. LF in most children without BPD within “normal range” though significantly ↓ cf. controls. Duration of O ₂ and FH asthma more predictive of subsequent FEV ₁ than GA.
Vrijlandt ¹²¹ The Netherlands	1983	42 PT (21% BPD)	81 FTC	27.1 (1.6) > 37	17.7 (1.2) 10.6 (0.4)	FEFV; BHR (MCh); BDR; ST	Y	Two birth cohorts each with own controls. Significantly ↓ FEV ₁ and ↑ BHR in PT versus FTC. Current BHR in PT associated with BPD and neonatal O ₂ . As partly mediated through FEV ₁ , structural sequelae rather than active inflammation possible mechanism.
McLeod ⁷¹ United Kingdom	1984	292 VLBW	48 FTC	30 (26–36) 37–42	19 (0.3) 21 (1.2)	FEFV; FRC _{pleth} Raw; DL _{CO}	Y	Mild ↓ in airway patency, DL _{CO} and exercise capacity in PT versus FTC, though insufficient to account for ↓ maximal exercise capacity.
Gross ¹¹² United States	1985–1986	96 PT (45% BPD)	574 class controls 108 FTC	Not given 28.2 (2.1) 40.1 (1.1)	8.8 (0.3) 8.8 (0.4) 7.0 7.0	FEFV; shuttle test FEFV; BDR; FRC _{pleth}	N Y	↑ Respiratory morbidity in VLBW cf. controls. Poorer LF associated with LBW, not IUGR. No difference in LF SGA versus AGA. ↑ Respiratory morbidity in those with BPD. LF ↓ in PT children with BPD versus no BPD. RV/TLC ↑ in PT (± BPD) versus FTC. BPD remained associated with AO and gas trapping after adjustment for BW and GA. CPET similar between groups.

(continued)

TABLE 1. (CONTINUED)

Author's details	Birth year	n (% BPD)	Controls n	GA (w)	Test age (year)	PFT outcomes	CPET	Comments/findings
Palta ⁷² United States	1988–1991	265 VLBW (22% BPD)	360	29 (2.5) > 37	10.4 (0.4) 9.6 (0.7)	FEFV		↓ FEFV in VLBW children, ± BPD at 10 years. No difference between those studied before or after routine surfactant therapy introduced. FEFV outcomes: BPD < PTC < FTC. Low FeNO and lack of BDR in most subjects suggest distinct pathophysiologic mechanism in children with BPD (not “typical” asthma’). Respiratory FU of subset of this cohort at 15 years suggests ↓ V'_{maxFRC} in infancy— primary risk factor for persistent AO. ↓ LF in ELBW children born in postsurfactant era versus FTC. Children with BPD worse LF than those without. Impaired exercise capacity despite only mild AO and gas trapping.
Baraldi ¹⁰⁸ Filippone ⁵⁷ Italy	1990–1994	31 BPD 31 PTC 17 BPD 17 PTC	31 FTC 34 FTC	28.6 (0.3) 28.9 (0.4) 40	8.6 (0.3) 8.6 (0.5) 8.7 (0.3) 15.0 15.0 15.0	FeNO; FEFV; BDR; ST FEFV; FRC _{pleth}	N	
Doyle ⁵⁹ Australia	1991–1992	240 ELBW (37% BPD)	208 FTC	26.7 (1.9) > 37	8.7 (0.3) 8.9 (0.4)	FEFV; FRC _{pleth} ; DL _{CO} 6 min walk; 20 m shuttle	N	
Smith ¹¹⁵ Australia	1992–1994	126 PT (29% BPD)	34 FTC	26.9 (1.7) 39.4 (1.2)	10.1 (1.1) 11.6 (0.8)	FEFV; BDR	N	
Fawke ⁶⁰ United Kingdom	1995	182 EP (71% BPD)	161 class controls	25.0 (0.7) > 37	10.9 (0.4) 10.9 (0.6)		N	FEFV outcomes: BPD < EP no BPD < FTC. 56% EP subjects abnormal spirometry (< LLN), 27% + ve BDR, and 25% “asthma.” Many asymptomatic EP with abnormal spirometry at 11 years.
Lum ⁶¹	1995	49EP (69% BPD)	52 class controls	24.9 (0.7)	11.2 (0.4)	LCI; FeNO; DL _{CO} FEFV; FRC _{pleth} ; sRaw BHR (MCh); ST	Y	All LF variables impaired except static LV among EP children versus controls, especially if prior BPD. FeNO and atopy similar between groups. 63% EP with FEFV outcomes < LLN. LCI and sReff abnormal in 58% and 45%, respectively. Significantly ↓ $\dot{V}O_2$ max; anaerobic threshold and peak workload in EP + altered breathing pattern during exercise. Physical activity similar, but very low in both groups. No difference in respiratory symptoms at ~5 years but PT children with prior BPD had impaired LF cf. no BPD. FOT, but not Rint, discriminated between PT children ± prior BPD.
Welsh ¹³⁶ United Kingdom		38/49 (71% BPD)	38/52	40.1 (1.6)	11.0 (0.5)	Physical activity		↓ Fat mass in BPD children with AO, though AO did not appear to be associated with ↑ resting energy expenditure. Rrs and Xrs worse in preschoolers with BPD versus controls. No difference in BDR. 77% success for FOT in BPD children (38% at 3 years; 78% at 4 years, and 100% at 5 years).
Vrijland ⁷³ The Netherlands	1998–2001	41 BPD 36 no BPD	73 FTC	28 (2) 29 (2) > 37	4.7 (0.8) 4.8 (0.8) 4.8 (0.8)	Rint; FOT (Rrs, Xrs) BDR	N	
Boff ⁶⁵ France	Not given	71 BPD	30 FTC	28 (2)	6.1 (1.1) 6.5 (1.2)	FEFV; BMI Body composition	N	
Thamrin ¹²⁷ Udomittipong ¹⁰⁴ Australia	1998–2002	49 BPD	78 FTC 158 FTC	26 [24–30] > 37	5.2 [3–6] 5.1 [4–5]	FOT (Rrs, Xrs) BDR	N	

Where data are available results have been summarized as Mean (SD) or Median [range] according to original publication.

For the purposes of this table we have used the authors’ description of birthweight criteria used for selecting their population but definition vary between publications. See original papers for details. AGA, appropriate for gestational age; AO, airway obstruction; BDR, bronchodilator response; BHR, bronchial hyperresponsiveness; BMI, body mass index; BPD, bronchopulmonary dysplasia; cf., compared with; CPET, cardiopulmonary exercise testing; DL_{CO}, diffusing capacity of the lung for carbon monoxide; EP, extremely preterm; ELBW, extremely low birth weight; FEFV, forced expiratory flow volume; FeNO, fractional exhaled nitric oxide; FEF_{25–75}, forced expiratory flow between 25% and 75% of FVC expired; FEFV_i, forced expiratory volume in 1 s; FH, family history; FOT, forced oscillation technique; FRC, functional residual capacity; FRC_{pleth}, functional residual capacity from plethysmography; FRC_N, FRC, single-breath nitrogen washout; FTC, full-term control; FVC, forced vital capacity; GA, gestational age; hist, histamine; IPPV, intermittent positive pressure ventilation; IUGR, intrauterine growth restriction; N, NO; LBW, low birth weight; LCI, lung clearance index; LF, lung function; LLN, lower limit of normal; LV, lung volume; MCh, methacholine; PFT, Pulmonary function test; PT, preterm; PTC, preterm control; raw, airway resistance; Rrs, respiratory system resistance; RV, residual volume; SGA, small for gestational age; sGaw, specific airway conductance; sRaw, specific airway resistance; ST, skin test; TLC, total lung capacity; VLBW, very low birth weight; V'_{maxFRC} , maximal flow at FRC; $\dot{V}O_2$ max, maximum oxygen consumption; Xrs, respiratory system reactance; Y, yes; +ve, positive.

Role of Lung Function Tests When Monitoring Children with Prior BPD

As BPD is classified during the neonatal period according to ongoing requirements for ventilatory support and supplemental oxygen, PFTs play no role in the diagnosis of BPD. They may, however, assist the clinician responsible for ongoing clinical management in children with persistent respiratory morbidity. In contrast to cystic fibrosis, wherein it has been shown to be relatively insensitive to mild or early lung disease,^{125,126} spirometry appears to be a more sensitive means of detecting deficits in lung function in children with BPD than other PFTs^{60,61} and would be the method of choice in children above 6 years. The reduced coordination and concentration in younger survivors of BPD means that assessments may need to be based on simpler tests, such as forced oscillation or interrupter techniques.^{73,104,127} It should be noted, however, that although such tests have an important role in clinical research studies, they may be far less discriminative in an individual child.

The types of question that a clinician may wish to address when assessing a child with prior BPD and the tests that would be appropriate to answer such questions are summarized in Table 2. Assessments such as bronchodilator re-

sponsiveness may identify the extent of airway obstruction reversibility or evidence of airway malacia; PFT pre- and poststandardized exercise test may provide evidence of exercise-induced bronchoconstriction; serial measurements of lung function over time may show effect of treatment, and skin test and assessment of exhaled nitric oxide may reflect airway inflammation. In severe cases, it may be necessary to refer the child for assessment of pulmonary hypertension.¹²⁸

Does the child have genuine superimposed asthma?

The main challenge for the clinician is to distinguish the consequences of prematurity and iatrogenic damage in the neonatal period (which are currently untreatable) from co-existent genuine eosinophilic asthma. Recently, it has been shown that exhaled breath temperatures and exhaled nitric oxide levels were significantly lower in BPD survivors than in asthmatic cases.¹²⁹ Defining atopic status with skin tests may be useful, because there would be a higher threshold for diagnosing true asthma in the nonatopic child. However, it is important to note that, when studying school-age full-term children, the same airway histology has been observed in nonatopic multiple-trigger wheezers as in atopic, multiple

TABLE 2. RELEVANT CLINICAL QUESTIONS WHEN ASSESSING RESPIRATORY STATUS IN A CHILD WITH PRIOR BRONCHOPULMONARY DYSPLASIA, AND APPROPRIATE TESTS TO ANSWER SUCH QUESTIONS

<i>Clinical question</i>	<i>Measurement conditions</i>	<i>Test(s)</i>	<i>Age group applicable</i>
Is the child atopic?		Skin test FeNO (offline analysis for <5 years)	Any age Any age
To what extent is airway obstruction reversible?	Assess bronchodilator (BD) response to β -2 agonist: Baseline PFTs, repeated 20 min postplacebo or no intervention, then 20 min post-BD.	sRaw, R_{INT} , or FOT Spirometry	4–6 years >6 years
Any evidence of airway malacia?	PFTs pre and post-BD to assess any adverse (paradoxical) response to β -2 agonist.	sRaw, R_{INT} , or FOT	4–6 years
Will inhaled corticosteroids (ICS) alleviate symptoms and improve lung function?	Baseline PFT and symptom questionnaire repeated after 1 month to assess repeatability and then repeated 3 months after trial of ICS	sRaw Spirometry	4–6 years >6 years
Does the child suffer from exercise-induced bronchoconstriction (EIB)?	PFT pre- and poststandardized exercise test (eg, shuttle test, cold air challenge)	Spirometry	>8 years
Why does the child have exercise intolerance?	EIB; physical activity levels. May also refer for assessment of motor coordination or more sophisticated hemodynamic measurements in special centers.	Spirometry VO_2 max; 7-day accelerometer	>8 years (depending on whether treadmill or bike used)
Is the child fit to fly?	SpO ₂ (pulse oximetry) in air and during 20 min in 15% FiO ₂ .	Hypoxic challenge	Any age

BD, bronchodilator; EIB, exercise-induced bronchoconstriction; FiO₂, fractional inspired oxygen; ICS, inhaled corticosteroids; R_{INT} , interrupter resistance; SpO₂, pulse oximeter oxygen saturation; VO_2 max, oxygen consumption during maximal exercise.

trigger wheezers,¹³⁰ emphasizing the importance of careful history taking and establishing precise wheezing phenotype.¹³¹ Spirometry and home peak flow monitoring should be used to document variable airflow obstruction, which is responsive to short-acting β -2 agonist and inhaled corticosteroids, before diagnosing “asthma.”¹³² The role of airway challenge testing in clinical practice in this group remains unclear.

Tracheo-bronchomalacia

This may occur in survivors of BPD and may be made worse by β -2 agonists. A bronchodilator trial using spirometry is therefore advisable before prescribing these medications. If the child is too young to perform spirometry, and no other test is available, careful auscultation of the chest should be performed before and after bronchodilator administration.

Does the child have exercise intolerance?

Many children with prior BPD may be relatively asymptomatic at rest, yet rapidly become breathless or wheezy on exertion.^{61,133–135} However, the pediatrician should be aware that nowadays many children are so sedentary that they rarely undertake sufficient exercise to cause breathlessness and that a negative response to questions regarding “shortness of breath” may be misleading.¹³⁶ Exercise testing may therefore be useful to obtain a more objective assessment of breathlessness on exercise. Measurement of oxygen consumption during maximal exercise may reassure unfit children (and their parents) that they can exercise safely. Equally importantly, such tests may diagnose exercise-induced bronchospasm, which, if treated appropriately, can greatly enhance fitness levels and quality of life.

Is the child fit to fly?

Although infant PFTs are not currently applicable for clinical management, the British Thoracic Society guidelines for air travel for infants and children with chronic lung disease recommend a preflight 20-min hypoxic challenge test and that such infants should not fly before 6 months corrected postnatal age.¹³⁷ These guidelines suggest that if pulse oximeter oxygen saturation falls below 90% on exposure to 15% inspired oxygen levels, supplementary in-flight oxygen is recommended. These cutoffs were, however, based on data from adults and older children and it has since been suggested that an pulse oximeter oxygen saturation <85% during the challenge may be more appropriate for infants and young children with BPD.¹³⁸ Nevertheless, although it has been ascertained that a significant percentage of preterm neonates do require in-flight oxygen supplementation, in its current form, the hypoxic challenge test does not accurately identify which infants are at risk for in-flight hypoxia.¹³⁹ Further adaptations of this test to ascertain whether hypoxia is primarily due to a shunt or ventilation-perfusion imbalance may eventually improve its diagnostic value.¹⁴⁰

Pulmonary hypertension may complicate BPD and is usually diagnosed echocardiographically rather than with invasive studies. The pathophysiological basis is likely multifactorial and include hypoplasia of the alveolar-capillary bed and vasospasm in areas of ventilation quotient mismatch. The classical picture in pulmonary arterial hy-

pertension without coexistent lung disease is normal spirometry and lung volumes, sometimes with mild restriction, but decreased diffusing capacity. However, normal lung function does not preclude pulmonary hypertension.¹⁴¹ It would appear reasonable to perform serial echocardiograms in all infants who are oxygen dependent, and err on the side of caution before weaning oxygen if there is any evidence of pulmonary hypertension.¹⁴²

Pediatrician's Role in Health Education

Recent studies on adolescent survivors of preterm birth have revealed a worryingly high prevalence of current smoking (~30% across all studies).^{59,120–122} Smoking-related problems are not limited to the subjects' own habits, such as whether or not they were subjected to *in utero* smoke exposure, which will further diminish reserves available,^{143,144} and whether they are regularly exposed to environmental tobacco smoke. Identification of reduced lung function and explanations regarding the need to preserve available capacity to enhance long-term health by avoiding smoking and adopting a healthy life style may prove beneficial for at least a proportion of these children and their families and should at least be addressed.

Limitations and Future Directions

Despite the overwhelming evidence that young adult survivors of BPD may be left with residual functional pulmonary abnormalities, there is currently limited respiratory surveillance of these individuals beyond infancy. Until these cohorts are followed up into middle age, it will be difficult to appreciate the full implications of these findings, but it is likely they will be at increased risk of developing early onset COPD,^{14,15} suggesting that closer attention to respiratory problems and implementation of appropriate treatment plans during childhood are required. In addition to deciding which tests to use, and how frequently such assessments should be made when caring for children with prior BPD, the clinician has to decide what is “normal” either in response to treatment or over time^{136,145–150} (see www.lungfunction.org and chapter x).

At the moment, we have no disease-modifying therapies for BPD. In the future, strategies for alveolar regeneration may become reality. There is increasing evidence for genetic susceptibility to BPD and also for important gene-by-environment interactions in susceptibility to altered lung function and the effects of tobacco smoke.^{41,42,151–164} Although these may enable us to identify high-risk groups, given the current lack of effective therapies, currently this may be of only theoretical importance.

Conclusions

In conclusion, despite their fragile status at birth, the majority of children surviving BPD do remarkably well once they cease to be oxygen dependent, such that, apart from the need for increased medications to control symptoms, cardiopulmonary problems are generally not a major health problem through the school years. Nevertheless, we cannot afford to be complacent because there is considerable evidence of long-term consequences, particularly during lung aging, that have yet to become fully apparent and such individuals are likely to present with an early, novel, COPD

phenotype. Consequently, increased clinical surveillance and follow-up throughout childhood, including strategic assessment of asthmatic status, bronchodilator responsiveness, and exercise testing, at least in those with ongoing symptoms, is warranted. With increasing survival following extremely preterm birth, BPD-associated adult lung disease is likely to become more common in future and should be included in the differential diagnosis of young adults, together with appropriate monitoring, treatment, and advice regarding preservation of existing lung reserves.

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