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Obstructive lung disease in children with mild to severe BPD

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Summary
Background: Bronchopulmonary dysplasia (BPD) is a common cause of respiratory insufficiency in children born very premature.
Objectives: The purpose of this study was to examine the impact of the severity of BPD on pulmonary morbidity at school age, as measured by conventional spirometry and impulse oscillometry. We also studied the association between changes in lung function and structural changes in the lungs of children with BPD via High-Resolution Computed Tomography (HRCT). Finally we studied the prevalence of atopy associated with BPD.
Methods: We studied 60 very low birth weight (VLBW) children, 28 with respiratory distress syndrome (RDS) who did not develop BPD ("preterm non-BPD") and 32 with RDS who developed BPD. The severity of BPD was graded as mild, moderate or severe. Follow-up at age 6–8 years consisted of spirometry, oscillometry, thoracic HRCT, allergy skin-prick test, blood samples and a questionnaire.
Results: All children with BPD showed some evidence of impaired lung function (more negative reactance, FEV1 $<$ 80% predicted, greater reversibility), although less than half of these children were symptomatic. The majority of children with BPD (19/26) showed abnormalities on HRCT. There was no evidence that atopy was associated with BPD.
Conclusions: Children with mild BPD exhibited similar impairments in respiratory mechanics and lung structure to those diagnosed with moderate BPD. The widespread involvement of the peripheral airways suggests that all children diagnosed with BPD are potentially at risk of developing chronic obstructive pulmonary disease later in life.

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Introduction

Bronchopulmonary dysplasia (BPD) is a common cause of respiratory insufficiency in children born very premature.[1,2] Despite the fact that the severity of BPD has declined over the past decade, the disease still leads to considerable long-term impairment of respiratory function.[3–5] Sequelae in childhood may be further aggravated by exposure to second-hand-smoking and/or by atopy. Over the longer term, infants with BPD may be at increased risk of developing chronic obstructive pulmonary disease (COPD) in adulthood.[6–12] Thus, systematic follow-up programs that include measurement of lung function are necessary to determine the severity of long-term lung impairment and to evaluate the efficacy of medical treatments. In this study, we examined the link between the severity of BPD in infancy and pulmonary morbidity at school age, as measured by conventional spirometry and impulse oscillometry. While both methods are non-invasive and require no sedation, the oscillometric method measures lung function during normal tidal breathing. Because it requires only minimal cooperation from the patient[5–14] compared with routine spirometry[15] oscillometry is particularly suitable for evaluating small children. Unfortunately, only a few studies have evaluated the concordance between the oscillometric and spirometric methods.[16–18]

When investigating the long-term effects of BPD, non-invasive imaging is valuable for identifying structural changes in the lung. High-resolution computed tomography (HRCT) is better at detecting these abnormalities than chest radiography, but its use in children with BPD is not widespread. Publications on this topic do, however, reveal pathological changes in the majority of the infant lungs examined.[19–23] Since children with BPD have similar clinical symptoms to children with asthma, the question of whether there is a correlation between BPD and atopy arises. Recent studies suggest that children with BPD do *not* have an increased prevalence of atopy (as do children with asthma).[24–26]

We hypothesized that: 1) the severity of BPD is the major factor determining whether respiratory abnormalities are present at school age; 2) findings based on oscillometry and spirometry may not agree because each technique describes different but complementary aspects of lung function; 3) there is an association between functional impairment and structural lung changes in children with BPD; and[4] 4)BPD is not associated with a higher prevalence of atopy at school age.

Materials and methods

Subjects

The study group consisted of 60 very low birth weight (VLBW) children, 28 with respiratory distress syndrome (RDS)[27] who did not develop BPD (preterm non-BPD group) and 32 with RDS *and* BPD. Mechanical ventilation and surfactant administration was initiated if the PCO2 exceeded 8.5 kPa, FiO2 $>$ 0.8 or BE ≥ -10 with signs of severe respiratory distress.

Those who did not develop BPD comprised a group against which the impact of BPD on lung function was compared. All children had been treated at the Neonatal Care Unit of Sachsska Children's Hospital between 1992 and 1997. For details, see Fig. 1.

The diagnosis of BPD was based on the need for supplementary oxygen at 28 days of age. The severity of BPD was determined at 36 weeks gestational age (GA) as follows: 1) breathing air - mild BPD; 2) need for supplementary oxygen (less than 30%) - moderate BPD; 3) $\geq$ 30% supplementary oxygen and/or continuous positive airway pressure (CPAP) or ventilator - severe BPD.[28]

Parents were fully informed about the purpose and procedures of the study and written informed consent was obtained. The study was approved by the Local Ethics Committee.

Perinatal and neonatal data included: treatment with prenatal steroids, GA at birth, birth weight (BW), instillation of surfactant, chest radiography at age 1 month, number of days on a ventilator, CPAP and supplemental oxygen.

Follow-up at 6–8 years

The questionnaire included questions about asthma, hay fever, eczema, the frequency of airway infections during the previous year, symptoms of airway hyper-reactivity, medical treatments, feeding difficulties, family history of atopy, and smoking habits of the family and the mother during pregnancy.

Physical examination: included measurements of body weight and height, allergy skin-prick test, blood samples, spirometry and oscillometry. Our Ethics Committee only granted approval for the BPD group to be scanned by HRCT.

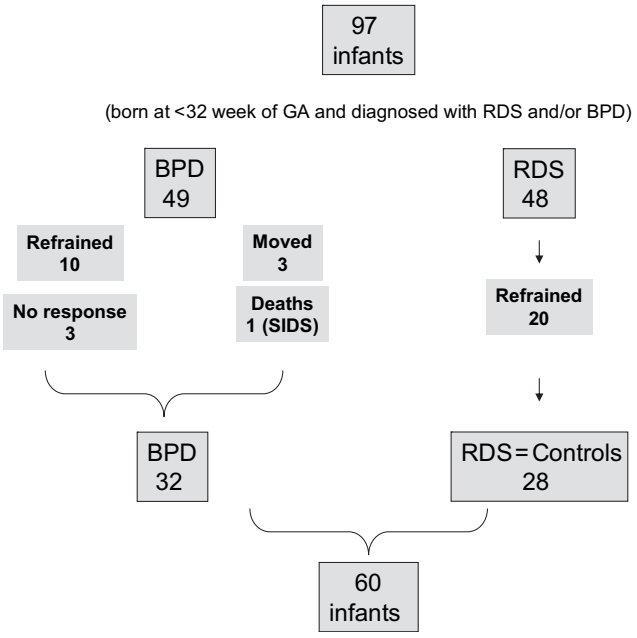

Figure 1 Schematic description of the recruitment into the study.

None of the children had respiratory infections at the time of the lung function tests. β_2-agonists were withdrawn 12 h beforehand. *Atopy* was defined as one or more positive skin-prick test results, defined as a weal with diameter $\geq$3 mm. The test panel involved 13 allergens: Alternaria, Cladosporium, Dermatophagoides farinae, Dermatophagoides pteronyssinus, dog, horse, rabbit, cat, birch, timothy, mugwort, hen's egg white, peanut. Histamine chloride (10 mg/ml) was the positive control and the allergen diluent was the negative control. Blood samples were taken and analyzed for eosinophil cation protein (ECP), IgA, IgG, IgM, and for airway and food allergens (Phadiatop; Phadia, Uppsala, Sweden).

Pulmonary function

Impulse oscillometry (IOS; Jaeger Masterscreen, Wűrzburg, Germany) was used to measure the input impedance of the respiratory system. The impulse interval was set to 0.3 s.[29] The reference values of Malmberg were used.[30] The pneumotachograph was calibrated daily before the use. The output pressure and flow signals were analyzed for resistance (R_{rs}) and reactance (X_{rs}), the two components of the respiratory impedance (Z_{rs}). Reactance is characterized by negative values i.e. the more negative the value the more pronounced is small airway dysfunction. The resonance frequency (fres Hz; the frequency at which X_{rs} is zero) was also calculated. The IOS measurements were performed with the child in a sitting position during tidal breathing. A nose clip was used and the cheeks were supported by the parent or investigator during measurements. A minimum of 20 s of regular breathing without sudden changes in online impedance was required. At least three measurements were performed and of these, three reproducible measurements were used to calculate mean values of R_{rs} and X_{rs} at an oscillation frequency of 5–35 Hz.

Dynamic spirometry to produce flow-volume curves was performed using a pneumotachograph (Vitalograph). Spirometry was done directly after the IOS measurement. A nose clip was used and the child performed the exhalation in a sitting position. At least three acceptable flow-volume curves were obtained according to the reproducibility criteria of the European Respiratory Society.[31] Forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), the ratio FEV_1/FVC (FEV%) and mid-expiratory flow at 75–25% of FVC (FEF_{75-25}) were recorded. Values of Polgar and Promadhat were used as reference data.[32]

Reversibility test: inhalation of 5 mg salbutamol by nebulizer (Ailos, Sweden) was given to the patient. Fifteen minutes after administration of the β_2-agonist, IOS and spirometry was repeated.

High-resolution computed tomography (HRCT) of the thorax

HRCT scans were performed on a four detector CT scanner (Siemens Volume Zoom) at 120 kV and 88–102 mA (depending on weight of the child) and a scanning time of 0.75 s. Approximately 20 HRCT images at 1.25 mm slice thickness and 10 mm intervals were evaluated. HRCT scans performed before 2002 were on a single detector CT scanner (HiSpeed Advantage, GE Healthcare) at 120 kV, 90 mA and a scanning time of 1.0 s. 10 HRCT images at 1 mm slice thickness and 10 mm intervals were evaluated.

Only two children required sedation during the examination.

Data analysis

- Differences between respiratory measurements of preterm non-BPD group and BPD groups were tested using Kruskal-Wallis analysis of variance and displayed graphically as Box-and-Whisker plots.
- Possible correlations between spirometric and IOS measurements were analyzed using linear regression analysis. The analysis comprised the entire study population i.e. no subgroup analysis was performed.
- Multiple regression analysis was used to analyze the influence of a variety of independent risk factors such as birth weight, gestational age at birth, days of oxygen treatment, steroids (systemic and inhaled), smoking and BPD on spirometric/IOS parameters. A forward stepwise regression was carried out to find factors that significantly contributed to variance.

P-values of <0.05 were considered significant.

Results

Perinatal and neonatal data

Of the total 60 children, 32 had BPD, of whom 20 were graded as mild, 8 as moderate, and 4 as severe BPD. The patient data are presented in Table 1a. The average BW and the GA of children with BPD was significantly lower than those without BPD. Children with mild, moderate or severe BPD were of similar BW and GA. The severity of BPD was positively correlated to days on a ventilator, CPAP and duration of days on supplemental oxygen.

Note that in the moderate group one child had supplementary oxygen for 28 days due to a ''late onset'' of need for oxygen, and the need for supplementary oxygen still at 36th week, therefore he was considered having moderate BPD. The min for the rest of the moderate group was 61 days.

Health status and symptoms at school age

There were no differences between age, height, weight and parental smoking habits at follow-up of children with and without BPD (Table 1b). Follow-up data on respiratory symptoms and medical treatments are provided in Table 2. None of the children were on systemic steroids. Only 1 infant in each group required hospitalization.

The prevalence of allergy among parents of BPD and non-BPD children was comparable (22/32 and 16/28 respectively, $p = 0.35$). On the other hand, significantly more parents of children with BPD suffered from asthma (16/32 and 7/28 respectively, $p = 0.047$).

Table 1 Population data — neonatal and follow-up data (60 infants).

	Non-BPD Median (min—max) $n = 28$	BPD Mild = 1 Median (min—max) $n = 20$	BPD Moderate = 2 Median (min—max) $n = 8$	BPD Severe = 3 Median (min—max) $n = 4$	Significance level p values
a					
Gestational age at birth (weeks)	30 (28—31)	27 (24—30)	27,5 (25—30)	28 (25—29)	<0.000 Non-BPD ≠ BPD1—3
Birth weight (g)	1495 (845—2094)	987,5 (654—1520)	1133 (597—1252)	905 (775—1210)	<0.000 Non-BPD ≠ BPD1—3
Instillation of surfactant	1	1	3	2	ns
Ventilatory therapy — duration (days)	0 (0—5)	0 (0—34)	3,5 (0—38)	23 0—33)	<0.000 Non-BPD = BPD1 ≠ 2—3
CPAP —duration (days)	3,5 (0—18)	31,5 (4—70)	32 (3—55)	32,5 (13—60)	<0.000 Non-BPD ≠ BPD1—3
Suplemental O_2 —duration (days)	3 (0—26)	55 (29—83)	71,5 (28*—96)	141 (105—180)	<0.000 Non-BPD ≠ BPD1 ≠ BPD2 ≠ BPD3
Smoking					
During pregnancy	8	3	3	4	Non-BPD = BPD
In home environment	8	5	3	4	
Any exposion	9	6	4	4	
Costicosteroids therapy					
Prenatal	18	13	5	2	Non-BPD = BPD
Systemic- postnatal	0	1	0	0	Non-BPD = BPD
b					
Smoking					
During pregnancy	8	3	3	4	Non-BPD = BPD
In home environment	8	5	3	4	
Any exposion	9	6	4	4	
Costicosteroids therapy					
Inhalation	0	12	6	4	Non-BPD ≠ BPD <0.000
Systemic	0	0	0	0	
Age at test (months)	91 (78—97)	88,5 (76—99)	87 (79—95)	85,5 (83—90)	ns 0.16
Height at test (cm)	127 (112—138)	124 (105—145)	120,5 (111—130)	122,5 (114—128)	ns 0.08
Weight at test (kg)	23,5 (19—31)	22 (15—42)	22 (17—29)	24 (19—26)	ns 0.78

- GA at birth — significantly higher in Non-BPD, no differences between BPD.
- Birth weight - significantly higher in Non-BPD, no differences between BPD.
- Ventilator (days) - BPD grade 2 and 3 similar, different from BPD grade 1 and Non-BPD.
- CPAP (days) - significantly lowest in Non-BPD, no differences between BPD.
- Suppl. O_2 — significant differences among ALL groups, highest in BPD 3.

* see explanation in the Results.

Lung function tests

The majority of children performed spirometry and oscillometry without difficulty although the IOS measurements for one child were inconclusive.

Since there were no significant differences between IOS, spirometry and reversibility results for children with mild and moderate BPD, pulmonary function data for these two groups were pooled and are presented as one entity (mild-moderate BPD).

Differences between spirometry/IOS results for children with and without BPD remained significant after adjustment for gestational age and birth weight. BPD was the strongest independent variable influencing lung function, contributing 16—40% to variability (Multiple Regression Analysis).

IOS

In general for children with severe BPD there was evidence of deterioration in lung function in all parameters tested (Table 3).

Spirometry

There were significant differences between preterm non-BPD group and children with mild-moderate and severe BPD for all parameters tested. Fig. 2 shows the results for all

Table 2 Follow-up data on respiratory symptoms, medical treatments and feeding difficulties.

	Non-BPD	BPD	Significance leves
Respiratory symptoms	5/28	15/32	$\mathbf{p = 0.02}$
>5 episodes with respiratory symptoms last year	1/28	5/32	$p = 0.12$
Asthma (as diagnosed by their doctor)	1/28	6/32	$p = 0.07$
Continuous inhalations with steroids	0/28	8/32	$\mathbf{p = 0.005}$
Treatment with β_2-agonists and steroids	0/28	5/32	$\mathbf{p = 0.03}$
Treatment with Montelucast	0/28	2/32	$p = 0.19$
Feeding difficulties	1/28	6/32	$p = 0.07$

four groups. Since there was no difference between mild and moderate BPD, the results for these groups are pooled together in Table 3.

Significantly more children with BPD had an FEV_1 below 80% predicted ($p < 0.001$). Only 8 of these 19 children described respiratory symptoms.

Reversibility test

A 10% increase in FEV_1 has been used as a positive result in the reversibility test. The most marked reversibility was found in children with severe BPD, followed by those with mild-moderate BPD and preterm non-BPD group (50%, 29% and 21% respectively). At the group level, irrespective of the severity of BPD, there was negative correlation between FEV_1% predictive and reversibility expressed in percent ($p = 0.00$, corr. coffecient $= -0.52$; see Fig. 3).

Concordance between spirometry and IOS

In absolute terms, there was a significant correlation between FEV_1 and resistance and reactance at 5–10 Hz ($p < 0.002$, $r = 0.43$–0.79) i.e. a low FEV_1 was associated with high resistance and high (more negative) reactance. There was better agreement for resistance at 5 Hz and FEV_1 ($p < 0.0003$, $r = 0.79$) than for the reactance values. Normalized values were tested using standard deviation (SD) for R and X at 5–10 Hz and percentage predicted FEV_1, ($p = 0.004$, $r = -0.37$).

Second-hand smoking and lung function

The prevalence of antenatal and/or postnatal exposure to cigarette smoke (second-hand smoking, SHS) was comparable between children with and without BPD. Twenty-three of 60 children were exposed to cigarette smoke either during fetal life or after delivery (Table 1). Fifteen mothers smoked during the entire pregnancy, and 3 stopped smoking during the first trimester. After delivery, 20 mothers either continued or resumed smoking. Children exposed to SHS had a significantly lower FEV_1% pred, FEV_1, FVC, and FVC % ($p = 0.04$, 0.05, 0.01, and 0.01, respectively) compared with non-exposed children. Respiratory reactance (Xrs5 and Xrs10) was also significantly higher (more negative) in smoke-exposed children ($p = 0.02$ and 0.02, respectively).

Immunology and atopy

Four children (2 in each group) refused to provide blood samples. ECP levels were not associated with spirometric findings ($p = 0.28$–0.95), or with the severity of BPD ($p = 0.21$). Six BPD and 5 control children refused a skin-prick test. Positive skin-prick tests were rare in both groups (5/23 and 3/21 in the control and BPD groups, respectively), as were positive Phadiatop tests (5/22 and 1/27 in the control and BPD groups; $p = 0.04$). Parental asthma did not affect a child's FEV1%pred. The children with clinical respiratory symptoms (wheezing, tachypne, retractions) did not differ with respect to FEV_1%pred from those who were asymptomatic.

There was a correlation between low FEV_1% pred and low levels of IgG ($p = 0.02$), but no correlation between FEV_1% pred and other immunological parameters.

Radiological findings

Twenty-five out of 32 chest radiographs taken at 1 month of age showed abnormalities. At follow-up at 6–8 years 4 families declined examination by HRCT and 2 had moved from the area of Stockholm. Of the total 26 successful HRCTs, 7 were normal, whilst 19 children showed minor abnormalities such as fibrosis, emphysema (10 children), bronchial wall thickening (2 children), and/or linear opacities (10 children). In mild BPD, 10/15 scans showed some abnormalities. In the moderate BPD group the proportion was 5/7, and in severe BPD emphysema was diagnosed in all children. Of the 19 children with abnormal scans, 11 had a $FEV_1 < 80\%$ pred.

Discussion

Children born premature, particularly those diagnosed with BPD, show increased morbidity during early childhood.[33] Studies have repeatedly demonstrated early impairment of lung function which may vary in severity during follow-up to adulthood. In the present study, we found reduced lung function at 6–8 years of age in children born premature who subsequently developed BPD. Functional lung impairment was most pronounced in severe BPD, but children with mild-moderate BPD also differed significantly from preterm non-BPD group. To assess the impact of BPD on lung function, our comparison group deliberately comprised preterm children with RDS that did not progress to BPD (preterm non-BPD group). Our study was *not* designed to evaluate whether preterm non-BPD group differed from healthy children born at term. In many follow-up studies, children with mild BPD have either been excluded or combined with preterm non-BPD group. The rationale for this was that the ''old'' definition of BPD was based on the need for

Table 3 Respiratory measurements with IOS and standard spirometry in children with BPD and non-BPD. The values represent medians (min-max).

	Non-BPD	BPD Mild = 1 Moderate = 2	BPD Severe = 3	*p* values
IOS				
Rrs 5 Hz kPa l^{-1} s^{-1}	0.7	0.8	1.0	0.01
	(0.5–1.0)	(0.5–1.3)	(0.7–1.1)	Non-BPD ≠ BPD1–2 ≠ BPD3
Rrs 10 Hz kPa l^{-1} s^{-1}	0.6	0.7	0.9	0.03
	(0.5–0.9)	(0.4–1.1)	(0.6–1.0)	Non-BPD = BPD1–2 ≠ BPD3
Rrs 15 Hz kPa l^{-1} s^{-1}	0.6	0.6	0.8	ns
	(0.4–0.8)	(0.4–0.9)	(0.5–0.9)	0.06
Rrs 20 Hz kPa l^{-1} s^{-1}	0.5	0.6	0.7	ns
	(0.4–0.7)	(0.3–0.8)	(0.46–0.8)	0.08
Xrs 5 Hz kPa l^{-1} s^{-1}	−0.2	−0.2	−0.4	0.03
	−0.4 to −0.2	−0.5 to −0.1	−0.4 to −0.3	Non-BPD = BPD1–2 ≠ BPD3
Xrs10 Hz kPa l^{-1} s^{-1}	−0.1	−0.1	−0.2	0.01
	−0.3 to −0.01	−0.3 to 0.0	−0.2 to −0.1	Non-BPD = BPD1–2 ≠ BPD3
Fres l/s	17	19	23	<0.005
	10–21	11–25	19–28	Non-BPD = BPD1–2 ≠ BPD3
Zrs 5 Hz kPa l^{-1} s^{-1}	0.7	0.8	1.1	0.01
	(0.5–1.1)	(0.5–1.4)	(0.8–1.2)	Non-BPD ≠ BPD1–2 ≠ BPD3
Spirometry				
FEV1L	1.5	1.2	0.9	<0.00
	1.1–2.1	0.8–1.9	0.7–1	Non-BPD ≠ BPD1–2 ≠ BPD3
FEV1%pred	95.4	81	68	<0.00
	75–111	61–97	44–71	Non-BPD ≠ BPD1–2 ≠ BPD3
FVC L	1.8	1.4	1.1	<0.00
	1.2–2.6	0.9–2.1	1–1.2	Non-BPD ≠ BPD1–2 ≠ BPD3
FVC %pred	98	85	74	<0.00
	78–129	66–109	54–89	Non-BPD ≠ BPD1–2 ≠ BPD3
FEV1L/FVCL	0.9	0.89	0.76	ns
	0.7–0.98	0.62–0.99	0.7–0.88	0.08
FEF 25–75%	93	66	42	<0.00
	44–123	31–107	19–123	Non-BPD ≠ BPD1–2 ≠ BPD3
Reversibility tests				
FEV1%rev	3.5	8.2	12.4	0.04
	0–22	0–24	1.4–30	Non-BPD ≠ BPD1–2 = BPD3
FEF 50%rev	8.7	25	38	0.01
	0–107	−3 to 96	13–72	Non-BPD ≠ BPD1–2 = BPD3
FEV 25–50%rev	13	23	38	ns
	0–126	0–114	−1.5 to 62	0.07
Rrs 5 Hz rev	21	26	24	ns
	0–39	0–46	12–35	0.7

supplementary oxygen at 36 weeks of GA. Our results, however, demonstrate that even children with mild BPD exhibit significant pulmonary dysfunction, and emphasize the need for careful diagnosis and follow-up of these children as a separate group.

Our study shows agreement between respiratory measurements performed by oscillometry and spirometry. Oscillometry is useful in identifying airway dysfunction e.g. bronchial obstruction, bronchial hyper-reactivity, and bronchodilator responsiveness,[1] and has the advantage of allowing measurements to be made during spontaneous tidal breathing. Moreover, because it requires minimal cooperation, oscillometry is ideally suited for children younger than 5 years, who are often difficult to study by conventional spirometry.

Impulse oscillometry

Our oscillometric findings - high resistance, and high (more negative) reactance for children with BPD - agree with published data. Malmberg et al. used the same impulse oscillometric system and studied children at the same age.[14] Like us, they found that oscillometry could differentiate children with and without BPD.

Our study further demonstrates that reactance at low frequencies is a highly sensitive marker of lung dysfunction

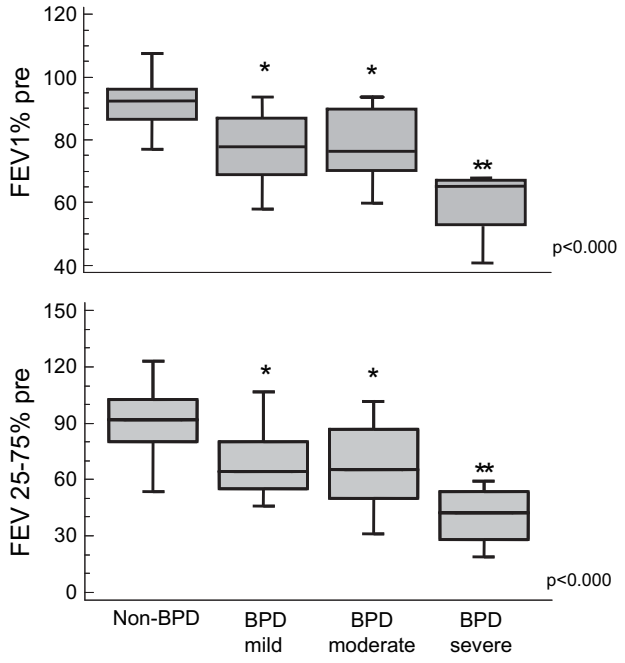

Figure 2 Spirometric measurements of FEV_1% predicted and FEV_{25-75}% predicted values in children at school age who suffered from neonatal lung disease of different grades. Notice the pronounced differences between the groups. Box-and-Whisker plot: the medians are presented as bold horizontal lines, the rectangles contain 50% of the values, the bars extend out to the minimum and the maximum values and the outlying values are presented as dots.

in prematurely born children, and may in fact differentiate the severity of BPD. Theoretically, reactance is mainly determined by peripheral obstruction and the elastic properties of the lung parenchyma, both of which are features of BPD. In our study, X10 was most negative in children with severe BPD. Thus X10 is a sensitive marker of lung changes after premature birth and may identify those children at risk of developing COPD.

In the present study the resistance at low frequencies was elevated in children with BPD. This finding contrasts

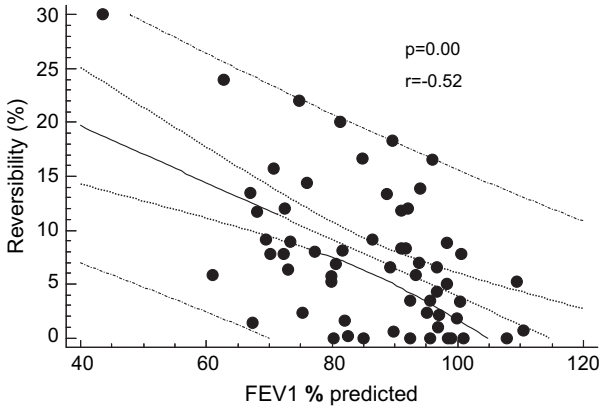

Figure 3 Association between individual FEV_1% predicted and reversibility (%) in the entire study population. The results show that children with most pronounced obstructivity were most sensitive to treatment with β2-agonists.

with recent data that suggested resistance was comparable but reactance and resonance frequency differed between children with and without BPD.[5]

Spirometry

Forced vital capacity (FVC % predicted) was within the normal range for our ''control'' children but was reduced in mild to severe BPD. This finding agrees with other studies that have demonstrated more-or-less normal lung volumes in healthy prematurely born children but slightly lower forced volumes in those with BPD. The reduction in FVC% could be due to restrictive lung function impairment and/or hyperinflation. FEV_1 is the most commonly used marker of obstructive lung disease and deteriorates slowly in progressive lung diseases such as COPD. Several follow-up studies on BPD at various ages have shown that FEV_1 may lie within the normal range (>80% predicted) but be slightly lower than in healthy controls.[3,35,36] We found that FEV_1 was significantly reduced in children with BPD. More importantly, at 6–8 years of age, half of the children with BPD had a FEV_1 below the normal range, compared with only about one-sixth of our preterm non-BPD group. This finding is consistent with data from others showing that BPD is associated with mild-to-moderately reduced lung function in early adulthood.[6,37] One study has, however, suggested the contrary: that there is some improvement in lung function between 7–10 years of age.[38]

Concordance between spirometry and IOS

Agreement between IOS and other methods of testing airway function has been described for asthma and BPD.[14] Malmberg et al. found the best association between FEV_1 and X5 in a group of prematurely born children, some of whom had BPD. This is consistent with our findings as well as studies of asthmatic children.[16,34]

On the basis of our results we conclude that both methods are useful for diagnosing obstructive disease although each describes different aspects of lung function (see below).

Reversibility test

Increased motor tone in bronchial smooth muscle has been shown in follow-up studies of BPD graduates.[6,37,38] Our data demonstrate significantly greater reversibility for children with BPD compared with preterm non-BPD group, with the greatest response seen in children with the most severe BPD. Oscillometry, on the other hand, failed to demonstrate reversibility differences between children with and without BPD.[5] Because reversibility can be detected by oscillometry in asthmatic patients,[35] it has been suggested by Vrijlandt et al., that airway damage may be more peripheral in BPD compared with asthma.[5]

HRCT findings

Pulmonary abnormalities were found in 72% of the children diagnosed with BPD during the neonatal period, with nearly 50% of these also suffering from emphysema. Because

emphysema results from disturbed alveolar and vascular development,[39] these children may be at risk of eventually developing COPD. Interestingly, most children with mild BPD (67%) showed similar anomalies to those with more severe forms of BPD.

Atopy

Children with BPD had respiratory symptoms, were classified as ''asthmatic'' and were treated with inhalation steroids and/or β_2-agonists to a much greater extent than controls. With regard to markers of atopy (ECP, positive skin-prick tests and positive Phadiatop), there were no differences between preterm non-BPD group and children with BPD. The prevalence of allergy among parents of these children was also comparable, although parents of children with BPD were more often asthmatic. Other studies have reported conflicting findings regarding the inheritance and prevalence of asthma in children with BPD.[26] These children have a different phenotype from that classically seen in atopic asthma, with normal levels of ECP and low prevalence of atopy. The higher prevalence of parental asthma in this group may reflect a hyper-reactive airway rather than atopy *per se*.

Conclusion

Our study reveals functional and structural pulmonary impairment but no signs of atopy in children suffering from mild as well as moderate and severe BPD. We found more marked impairment at the severe end of the BPD spectrum. The long-term importance of these changes, which include reduced FEV_1 and an abnormal IOS result, is not yet clear. The abnormal IOS result we and others have reported may reflect peripheral and possibly more widespread airway impairment, as also suggested by HRCT. From a clinical perspective, these children (especially those most severely affected) could be at high risk of developing chronic lung disease later in life. There have been few, if any, prospective studies on treatment and other interventions after the neonatal period. Functional and imaging techniques that can differentiate the more severe from milder forms of airway impairment could play an important role in the early evaluation of preschool children with BPD. Early and accurate evaluation may lead to improved intervention and treatment to reduce the risk of further deterioration. Clearly, all children with BPD, regardless of its severity, should be followed clinically. More detailed long-term follow-up is needed to characterize the pulmonary sequelae, improve treatment and reduce the incidence of COPD.

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Conflict of interest statement

The authors hereby declare that there is no conflict of interest.

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