PNEUMOLOGY

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Response to bronchodilators in clinically stable 1-year-old patients with bronchopulmonary dysplasia

Abstract Bronchodilators are often used in the treatment of patients with bronchopulmonary dysplasia (BPD). However, few studies evaluate their efficacy in patients with stable disease beyond the newborn period. Therefore, pulmonary function was measured before and after aerosol treatment with salbutamol (0.25 ml Ventolin 0.5%) and subsequently after aerosol with ipratropium bromide (0.25 ml Atrovent 0.025%). Studies were performed at the corrected postnatal age of 52 ± 2 weeks in 52 patients who had been ventilated after birth because of newborn lung disease. Twenty-two of these 52 patients had developed BPD. Pulmonary function was measured after sedation and using the PEDS system. Expiratory resistance (median 52.1 versus 39.1 cmH$_2$O/l/s; $P < .008$) and inspiratory resistance (median 42.5 vs 27.8 cmH$_2$O/l/s; $P < .04$) were significantly worse in BPD patients at the age of 1 year. Half of the BPD patients had a decrease in pulmonary resistance after salbutamol. However, there was no statistically significant decrease in pulmonary resistance after salbutamol or ipratropium in the BPD patients as a group. After salbutamol pulmonary resistance significantly worsened in the patients who did not develop BPD.

Conclusion Although individual patients may benefit, routine administration of bronchodilators seems not warranted in stable BPD patients at the age of 1 year.

Key words Bronchopulmonary dysplasia Bronchodilators · Pulmonary function

Abbreviations *BPD* bronchopulmonary dysplasia

Introduction

In patients with BPD, an improvement in pulmonary mechanics after administration of bronchodilators has been well documented in the acute stage of the disease [2, 3, 7, 9, 17, 21]. Therefore it has been suggested that long-term treatment with bronchodilators may be beneficial [2, 5, 7, 17].

Because only few data evaluate the response to bronchodilators in infants in a more chronic, stable phase of the disease, we measured pulmonary function before and 15 min after administration of salbutamol and ipratropium bromide in patients with BPD and without BPD at the corrected postnatal age of 1 year.

Patients and methods

The series consisted of 105 consecutive infants with neonatal lung disease necessitating artificial ventilation and admitted to the neonatal intensive care nursery of the University Hospital of Leuven during 1989. Seventy infants (67%) survived their neonatal disease. One of them subsequently died. At the corrected postnatal age of 1 year, 52 of the remaining 69 patients could be traced and consented to participate in the follow up study. Initial indication for artificial ventilation included respiratory distress syndrome only (36 patients) or pneumonitis, meconium aspiration, wet lung syndrome and postasphyxic pulmonary oedema often in addition to respiratory distress syndrome (16 patients). Twenty-two patients (42%) had developed BPD, defined as respiratory symptoms and oxygen dependence beyond 28 days of age in association with an abnormal chest radiograph. The subjects who met the diagnostic criteria for BPD constituted the study group. Control infants were the remaining 30 patients who survived and did not meet the cri-

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teria for BPD. Median and quartile ranges for birth weight were 1300 g (980–1880) in the BPD group, and 1825 g (1460–2400) in the control group. Median and quartile ranges for duration of artificial ventilation were 9 days (5–19) in the BPD group and 4 days (3–5) in the control group. Median and quartile ranges for duration of oxygen administration were 67 days (52–88) in the BPD group and 9 days (7–16) in the control group.

The patients were studied at the corrected postnatal age of one year (+2 weeks) and at least 2 weeks following the last episode of respiratory tract infection. Family history of asthma, atopy in first or second degree relatives, previous episodes of wheeze and hospital admissions for respiratory disease were noted.

The tests of pulmonary function were performed in sleeping infants lying in a supine position. Chlorpromazine (Largactil 1 mg/kg), promethazine (Phenergan 1 mg/kg) and sodium pentobarbital (5 mg/kg) were administered 30 min prior to each study. The routine use of chloralhydrate was changed to the above mentioned drugs, because sedation after chloralhydrate was too short to allow patients to be studied after both aerosol treatments.

Studies were performed during sleep when regular breathing was observed. Throughout the study period the patient's head was kept in the midline position, while the jaw was supported. Pulmonary function tests (minute volume, dynamic lung compliance, in- and expiratory pulmonary resistance) were performed with a commercially available, computerised system (PEDS, MAS, Inc., Hatfield, Pa.). Airflow was measured by means of a Fleish 0 pneumotachograph and a differential pressure transducer (Model MP45, Validyne Engineering Corp., Ca.). These devices were attached to a face mask. Tidal volume was determined for each breath by integration of the flow signal. A Mallinckrodt air-filled oesophageal balloon was placed in the distal oesophagus and its position checked by observing the online pressure tracing [19]. The mask and the oesophageal balloon's position or volume were changed when necessary. Usually 0.4 ml was adequate to obtain the balloon's working range as described by Stocks and Coates [19]. A Colesco P7D differential pressure transducer measured transpulmonary pressure changes as the difference between airway and oesophageal pressure. At end-expiration, the pneumotachograph was manually occluded and the pressure, flow and volume tracings were examined to exclude any leaks and to assess that during occlusion the pressure transducer output was zero. Pulmonary mechanics and energetics were determined by using the least mean square analysis technique [20]. Simultaneous recordings of airflow, volume and transpulmonary pressure were sampled and recorded at a rate of 75 Hz per channel. Breaths were accepted for analysis if they met the criteria described by Lorino et al. [13]. A minimum of 20 breaths per test were evaluated.

Salbutamol (sol 0.5% Ventolin) 0.25 ml was nebulised with 3 ml of normal saline via a Hudson updraught nebuliser attached to a face mask. The drug was administered with a flow of 8 l/min for 5 min. Pulmonary function tests were repeated 15 min after the drug administration. Subsequently an aerosol with 0.5 ml of ipratropium bromide (sol 0.025%; Atrovent) was given and pulmonary function was again measured 15 min later.

The study was approved by the ethical committee of the hospital.

Data are expressed as median and quartiles because data distribution was not always normal. Differences between the two groups were evaluated using the chi square test, the non parametric test of Mann-Whitney-U or the Wilcoxson matched pairs signed ranks test as appropriate. They were considered as significant for $P < 0.05$.

Results

Median and quartiles for gestational age at birth and weight at follow up study are given in Table 1.

A positive family history of atopy was not significantly more frequent in the BPD patients than in non BPD patients. Recurrent wheeze during the 1st year of life occurred in 13 of 22 BPD patients compared to 9 of 30 controls ($P = 0.04$). Readmission to hospital after initial discharge was not significantly more frequent: 5 of 22 patients with BPD versus 4 of 30 controls.

Results for pulmonary function tests are given in Table 1. Adequate pulmonary function data were obtained in 22 BPD babies at baseline, in 18 after administration of salbutamol and in 17 patients after administration of ipratropium bromide. All three tests could be performed in 15 infants. Adequate pulmonary function data were obtained in 29 control babies at baseline, in 22 after administration of salbutamol and in 16 after administration of ipratropium bromide. The parents of 4 control patients refused that their infants were studied after drug administration. All three tests could be performed in 16 control infants.

Inspiratory and expiratory pulmonary resistance were significantly higher in BPD patients ($P < 0.05$). Dynamic pulmonary compliance was lower in BPD patients but the difference was not statistically significant (Table 1).

After administration of salbutamol, there was no significant change in minute ventilation, inspiratory or expiratory pulmonary resistance or dynamic pulmonary compliance in the BPD patients (Table 2). There was also no significant change of these parameters 15 min after ipratropium bromide (Table 2). There was also no significant change in pulmonary resistance when only BPD patients with recurrent wheeze in the past were considered. When assessed in an absolute way, 9 patients had improved pulmonary resistance (median improvement 19.5 cmH$_2$O/l/s; P25 and P75 9.5–29.8 cmH$_2$O/l/s) and 9 patients had worse pulmonary resistance (median deterioration 14.9 cmH$_2$O/l/s; P25 and P75 6.6–22.9 cmH$_2$O/l/s (Fig. 1). The change after bronchodilator was not related to sex, gestational age, history of atopy or wheeze, clinical severity or initial pulmonary function. The 95th percentile for intra-patient variability of airway resistance measurement in our pulmonary function laboratory is 18%. A change larger than 18% may therefore be considered as significant.

Table 1 Median and quartile values for gestational age at birth, weight and pulmonary function data in patients with and without BPD

|	BPD ($n = 22$)		NO BPD ($n = 30$)	
Gestational age (weeks)	28*	(27–32)	32	(31–34)
Weight (kg)	8.8*	(7.9–9.8)	9.7	(9.1–10.5)
Minute ventilation ml/kg/min	261	(225–307)	246	(218–285)
Inspiratory resistance cmH$_2$O/l/s	42.4*	(30–54.9)	27.8	(22.6–45.0)
Expiratory resistance cmH$_2$O/l/s	52.1*	(39.6–66)	39.1	(29.3–51.9)
Dynamic compliance ml/cmH$_2$O/kg	1.46	(1.22–1.70)	1.65	(1.34–1.84)

*$P < 0.05$ by Mann-Whitney-U test

Table 2 Median and quartile values for pulmonary function in the BPD patients before and after bronchodilator (salbutamol sol 0.5% 0.25 ml; ipratropium bromide sol 0.025% 0.5 ml)

	Baseline $n = 15$		After salbutamol $n = 15$		After ipratropium $n = 15$	
Minute ventilation (ml/min/kg)	239	(224–305)	256	(209–292)	250	(213–290)
Inspiratory resistance (cmH$_2$O/l/s)	47.8	(32.3–54.9)	40.4	(29.1–58.3)	46.6	(35.8–65.6)
Expiratory resistance (cmH$_2$O/l/s)	61.9	(37.1–75.7)	49.8	(34.1–73.7)	53.1	(41.7–86.8)
Dynamic compliance (ml/cmH$_2$O/kg)	1.41	(1.13–1.53)	1.45	(1.12–1.66)	1.26	(1.01–1.83)

Seven patients had no significant change after salbutamol; six had a significant improvement and five had significant worsening (Fig. 1).

In the control group there was a significant increase in inspiratory and expiratory pulmonary resistance after administration of salbutamol (Table 3). Pulmonary resistance after salbutamol deteriorated significantly only in patients who had not had recurrent wheeze ($n = 15$) (Table 4). In the patients who had had wheeze in the past ($n = 7$), pulmonary resistance after salbutamol did not change. There was no further change in pulmonary function after administration of ipratropium bromide.

Discussion

Abnormal pulmonary function in BPD patients at follow up has been reported in several studies [4, 8, 18]. Also in the present study pulmonary resistance was significantly higher in infants with BPD when compared to those ventilated for neonatal lung disease who did not develop BPD. However, in the present study there was no improvement in pulmonary resistance after inhalation of bronchodilators. Many studies have evaluated the response to bronchodilators in very early BPD when

Fig. 1 Expiratory airway resistance after salbutamol (expressed as percentage change from baseline) compared to the initial expiratory airway resistance in BPD patients. There is no correlation between baseline expiratory pulmonary resistance and the change after salbutamol. Expiratory airway resistance at baseline is expressed in cmH$_2$O/l/s. The *dotted lines* (+ and −18%) indicate the 95th percentile for intra-patient variability of the expiratory airway resistance measurement in our pulmonary function laboratory
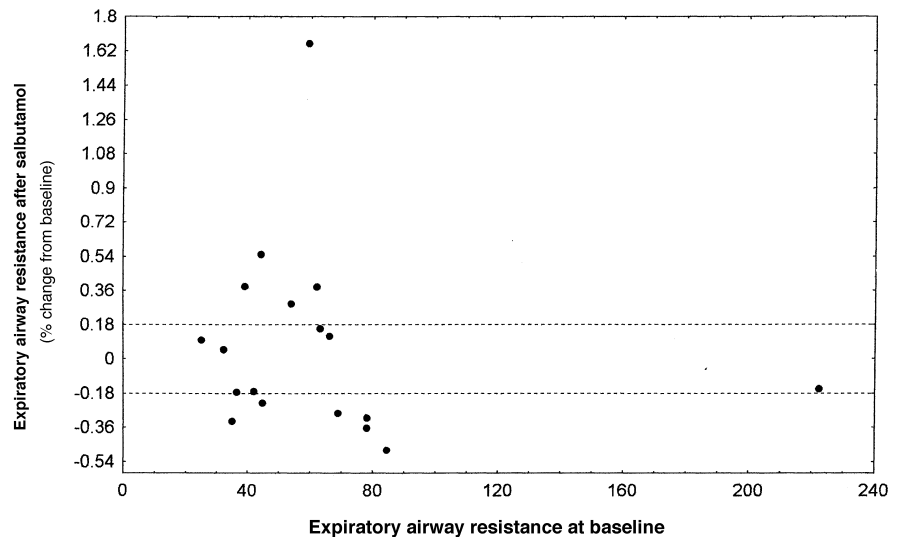
Table 3 Median and quartile values for pulmonary function in the control patients before and after bronchodilator (salbutamol sol 0.5% 0.2 ml, ipratropium bromide sol 0.025% 0.5 ml)

	Baseline $n = 16$		After salbutamol $n = 16$		After ipratropium $n = 16$	
Minute ventilation (ml/min/kg)	232	(212–280)	250	(209–275)	245	(202–273)
Inspiratory resistance (cmH$_2$O/l/s)	27.3	(21.5–46.6)	38.4	(25.5–54.4)*	46.4	(32.6–62.6)
Expiratory resistance (cmH$_2$O/l/s)	38.6	(30.1–55.6)*	49.6	(35.6–69.4)*	56.0	(35.3–65.4)
Dynamic compliance (ml/cmH$_2$O/kg)	1.68	(1.29–2.00)	1.68	(1.40–2.18)	1.58	(1.40–1.84)

*$P < 0.05$ by Wilcoxson matched pairs signed rank test

Table 4 Median and quartile values for pulmonary resistance in the control patients without recurrent wheeze, before and after administration of salbutamol (sol 0.5% 0.25 ml)

	Baseline $n = 15$	After salbutamol $n = 15$
Inspiratory resistance (cmH$_2$O/l/s)	27.8 (22.4–46.9)	43.5 (35.3–57.1)*
Expiratory resistance (cmH$_2$O/l/s)	51.8 (37.6–61.6)	61.5 (43.8–70.0)*

*$P < 0.05$ by Wilcoxson matched pairs signed rank test

patients are still being ventilated [2, 3, 7, 9, 17, 21]. In these ventilated babies improvement of pulmonary compliance and airway resistance has been reported after beta mimetic and anticholinergic drugs but also after administration of caffeine [18], aminophylline [8] and diuretics [4]. Roocklin et al. [16] evaluated the effect of theophylline on pulmonary function in nine BPD patients and reported improvement only in patients younger than 1 month. Therefore, age may be an important factor when evaluating the response to bronchodilators. The authors suggest that theophylline is probably most effective in the younger infants in whom there is less pulmonary fibrosis.

Only a few studies assessed the effect of bronchodilators in older non ventilated BPD patients. Logvinoff et al. [12] measured pulmonary resistance in six BPD patients 4–43 months old and found no significant change after administration of isoproterenol. Kao et al. [10, 11] reported two studies. In one study [10], ten BPD patients and 16 control patients were studied at a postnatal age of $41 + 1$ weeks disclosing a mean decrease of 28% of pulmonary resistance after administration of isoproterenol. In the second study [11], pulmonary resistance was measured in 15 BPD patients at a mean postnatal age of 16 weeks (range 4–28 weeks) and a similar decrease in airway resistance was reported after administration of metaproterenol and atropine. All infants in these studies were recruited from an in-hospital population. Nine of the 15 patients in the first study were still on oxygen therapy. The BPD patients in the present study formed a homogenous group: they were all born in the same year, they were all treated at the same hospital, they were all studied at the corrected postnatal age of 1 year and at least 14 days after an episode of respiratory tract infection. At the time of the study they were all being cared for at home. It is likely that during this stable period, residual fibrosis is more important than reactive airway disease.

Smyth et al. [18] evaluated the response to bronchodilators in eight BPD patients with a mean age of 8.4 years and reported improvement in 1 s forced expired volume in five children and a decrease in the same parameter in the three other children. The study is descriptive, without a control group. The results are not that different from our findings: indeed, half the patients had an improvement in pulmonary resistance in the present study (Fig. 1). Northway et al. [14] evaluated response to bronchodilators in adolescents and young adults with BPD and reported airway reactivity assessed by response to bronchodilator or metacholine challenge in half of their 25 patients. About a quarter of the patients had fixed airway obstruction.

An interesting finding in the present study is the worsening of pulmonary function in control infants without BPD. Yuksel et al. [22] reported worsening of pulmonary resistance after administration of ipratropium bromide in premature infants with recurrent wheeze who were asymptomatic at the time of the study. O'Callaghan et al. [15] observed paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. In the present study, distinct worsening of pulmonary resistance occurred only in patients who did not have recurrent wheeze. The cause is unknown. Airway reactivity induced by administration of aerosol due to acidity or hypo-osmolarity of the solution is possible. Some degree of bronchomalacia worsened by bronchodilator administration may also play a role.

Other tests than airway resistance measurements may be of value to assess changes in pulmonary mechanics after bronchodilator administration. In the present study we did not measure the maximal expiratory flow at functional residual capacity using the squeeze jacket technique. This variable may be more sensitive than the airway resistance measurement to detect abnormalities in BPD patients [1]. We have recently shown that the shape of the tidal flow volume loop correlates well with measurements of pulmonary mechanics [6] but in the present study we have not analysed the shape of the tidal loop before and after bronchodilator.

Bronchodilators have been reported to cause tachycardia in BPD infants [17]. Other possible side-effects include agitation, tremor, hypertension, hyperglycaemia and increased metabolic rate [3]. Also in view of our present knowledge on the possible deleterious effect of continuous administration of bronchodilators to patients with asthma, and taking into account the results of the present study, there are probably no valid reasons to administer bronchodilators to all patients with BPD. Indications may be early disease in selected patients or with acute exacerbations and worsening wheeze during an upper respiratory tract infection.

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