Eur Respir J
1991, 4, 1088–1092

Effect of nebulized salbutamol in preterm infants during the first year of life

B. Yuksel, A. Greenough

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ABSTRACT: The acute effect on lung function of nebulized salbutamol and saline (placebo) has been investigated in preterm infants at follow-up. Twenty two premature infants, median gestational age 29 weeks (range 26–32 weeks) and birthweight 1,264 g (720–1,800 g), were studied at a median postnatal age of 7 months (range 6–9 months). Nine of the infants had recurrent respiratory symptoms; they coughed and/or wheezed at least 3 days per week for the previous 4 weeks. The remaining 13 infants were free from recurrent or persistent respiratory symptoms. Thoracic gas volume (TGV) and airways resistance (Raw) were measured and specific airway conductance sGaw calculated before and 10 min after salbutamol and normal saline given *via* a nebulizer. Amongst the symptomatic infants administration of nebulized salbutamol was associated with a median reduction in Raw of 25% ($p<0.01$) and also a significant improvement in sGaw ($p<0.01$). In the asymptomatic infants neither Raw nor sGaw changed significantly. Nebulized saline caused no significant change in lung mechanics in either the symptomatic or asymptomatic infants. We conclude that nebulized salbutamol is an effective bronchodilator for symptomatic preterm infants less than one year of age.

Eur Respir J., 1991, 4, 1088–1092.

Dept of Child Health, King's College Hospital, London, UK.

Correspondence: A. Greenough, Dept of Child Health, King's College Hospital, London SE5 9RS, UK.

Keywords: Bronchodilator; lung function; plethysmography; prematurity.

Received: July 11, 1990; accepted after revision June 6, 1990.

B.Y. is supported by the Joint Research Council of King's College Hospital.

Many preterm infants have recurrent respiratory symptoms, such as wheeze and cough, at follow-up [1–4] but very few that we reviewed had received specific therapy [5]. Nebulized salbutamol has been used effectively in older children to treat such symptoms [6–8], but the efficacy of this treatment in infants of less than two years of age remains unclear. Although it had been suggested that infants less than 18 months old do not respond to nebulized bronchodilator [9], more recently it has been demonstrated that wheezy infants do have functioning $beta_2$-receptors and, thus, may respond to salbutamol [10]. Nebulized salbutamol has been shown to protect against the deterioration in lung function caused by nebulized water in infants less than one year of age [11].

Bronchodilator therapy may be even more effective in infants born preterm, as its administration has been associated with improvements in lung mechanics even in very young infants still receiving intensive care. A beneficial response has been described both in ventilated infants [12, 13] and amongst infants with bronchopulmonary dysplasia (BPD) [14, 15]. There is, however, very little information as to the efficacy of bronchodilator therapy for preterm infants at follow-up.

We have previously demonstrated that maintenance therapy with inhaled salbutamol, administered *via* a spacer device, reduces symptoms and improves lung function in preterm infants less than two years of age [16]. During admission or for severe symptoms at home, however, bronchodilator therapy is likely to be given *via* a nebulizer, as during wheezing attacks the successful use of a metered dose inhaler is unpredictable in this young age group [17]. The aim of this study, therefore, was to determine the acute effect of nebulized salbutamol on lung function in preterm infants at follow-up.

Patients

Twenty two preterm infants were enrolled into the study. Twelve girls and 10 boys, median birth weight of 1,264 g (range 720–1,800 g) and gestational age 29 weeks (range 26–32 weeks), were studied at a median postnatal age of seven months (range 6–9 months). The infants had all required respiratory support for respiratory distress syndrome in the neonatal period at King's College Hospital (KCH). Three infants had required an increase in the inspired oxygen concentration only, but the remaining 19 infants had been ventilated (6 for less than one day, 9 for 1–7 days, and 4 for more than 7 days).

Nine of the infants had recurrent respiratory symptoms: they coughed and/or wheezed on at least three days per week for the previous four weeks. The remaining 13

infants were asymptomatic. The median birth weight and gestational age of symptomatic and asymptomatic infants are shown in table 1. No infant was receiving treatment at the time of entry into the study.

Ethical permission for this study was granted by King's College Hospital's Ethics Committee.

Table 1. – Symptomatic and asymptomatic infants with their characteristics

	Symptomatic	Asymptomatic
Birthweight g	1300 (720–1640)	1210 (840–1800)
Gestational age weeks	29 (26–31)	29 (26–32)
Postnatal age months	7 (6–9)	7 (6–9)
Female/male	5/4	7/6

Data given as mean and range in parentheses.

Methods

The infants were seen in the Paediatric Respiratory Laboratory where height and weight were recorded and the infants examined. Sedation was achieved with oral chloral hydrate (100 $mg \cdot kg^{-1}$). Thoracic gas volume (TGV) and airway resistance (Raw) were measured during quiet sleep, in a whole body plethysmograph. Specific airway conductance (sGaw) was calculated from TGV and Raw. Measurements were made before and 10 min after nebulized normal saline (3 ml) or salbutamol (2.5 mg in 3 ml of normal saline) given in random order on separate occasions. Normal saline or the salbutamol solution was administered *via* a mini-Neb nebulizer (Bard Ltd) using an inspiron compressor (Bard Ltd) with a flow rate of 8 $l \cdot min^{-1}$ for 4 min.

Lung function measurements

During the measurements the infants breathed through a face-mask which was sealed around the nose and mouth with a silicone putty to ensure an airtight seal. The servo-controlled heating system maintained the face-mask and humidified rebreathing bag at 36°C. TGV was measured at the end of inspiration and Raw at two thirds of inspiratory flow as previously described by RADFORD [18] and DUBOIS *et al.* [19, 20]. TGV was calculated from five breaths during occlusion and at least five occlusions were made. Raw was calculated from a minimum of 10 breaths when flow and pressure signals were in phase. Flow, volume, box and mask pressure changes were simultaneously recorded on ultraviolet recording paper. All of these plethysmographic traces were then analysed blind of clinical details by one observer. The measurements were corrected for apparatus deadspace (15 ml) and resistance (8 $cmH_2O \cdot l^{-1} \cdot s$ measured at flows between 5–20 $l \cdot min^{-1}$).

The reproducibility of TGV and Raw measurements were assessed by repeated measurements in 16 infants of similar gestational age and postnatal age to the study population. The coefficient of variation of TGV and Raw was calculated from at least five measurements before and after infants had been removed and returned to the body plethysmograph. The coefficient of variation was 6% for TGV and 9% for Raw, hence a statistically significant change for Raw was defined as greater than 18%. sGaw was calculated from the results of TGV and Raw obtained in the reproducibility study, this gave a coefficient of variation for sGaw of 8%.

Statistical analysis

A paired Wilcoxon Rank Sum test was used to assess whether differences in lung function before and after administration of the nebulized solutions were significant.

Results

At the start of the study the median TGV was 35.2 $ml \cdot kg^{-1}$ (range 25–53 $ml \cdot kg^{-1}$) and Raw 38 $cmH_2O \cdot l^{-1} \cdot s$ (range 25–95 $cmH_2O \cdot l^{-1} \cdot s$) in the 22 infants. Raw tended to be higher in symptomatic infants compared to the asymptomatic infants at the start of the study (table 2) but this did not reach statistical significance. All infants successfully completed the study, with none waking between the two measurements.

Raw decreased following the administration of bronchodilator by a median of 25% in the symptomatic infants ($p<0.01$) and there was a statistically significant reduction in eight of nine infants (table 2 and fig. 1). In the asymptomatic infants, Raw decreased only by a median of 6% following the bronchodilator with a statistically significant reduction in Raw in only one child (fig. 1). In four of the asymptomatic children, Raw increased following bronchodilator, but only in one child was this statistically significant. Neither the symptomatic nor the asymptomatic group had a statistically significant change in TGV in response to bronchodilator. sGaw increased in the symptomatic infants after salbutamol administration ($p<0.01$) but there was no significant change in the asymptomatic infants (fig. 2).

Following the administration of normal saline, Raw increased by a median of 4.5% in the asymptomatic infants and decreased by 4.5% in the symptomatic infants, neither of these changes were statistically significant (table 3). Only one infant, who was asymptomatic showed a statistically significant change in Raw (an improvement), this child had had a similar response to the bronchodilator. There was no significant change in TGV or sGaw following saline administration in either group (table 3).

Table 2. – Lung function measurements before and after bronchodilator

	Symptomatic infants		Asymptomatic infants	
	Pre	Post	Pre	Post
TGV ml·kg^{-1}	32 (25–54)	32.6 (18–52)	39 (25–47)	37 (27–43)
Raw cmH$_2$O·l^{-1}·s cmH$_2$O·l^{-1}·s	46 (25–95)	32 (18–70)	32 (17–68)	30 (16.5–77)
sGaw cmH$_2$O^{-1}·s^{-1}	0.13 (0.06–0.22)	0.17 (0.09–0.30)	0.109 (0.06–0.33)	0.12 (0.07–0.36)

Data are given as mean and range in parentheses. TGV: thoracic gas volume; Raw: airway resistance; sGaw: specific airway conductance.

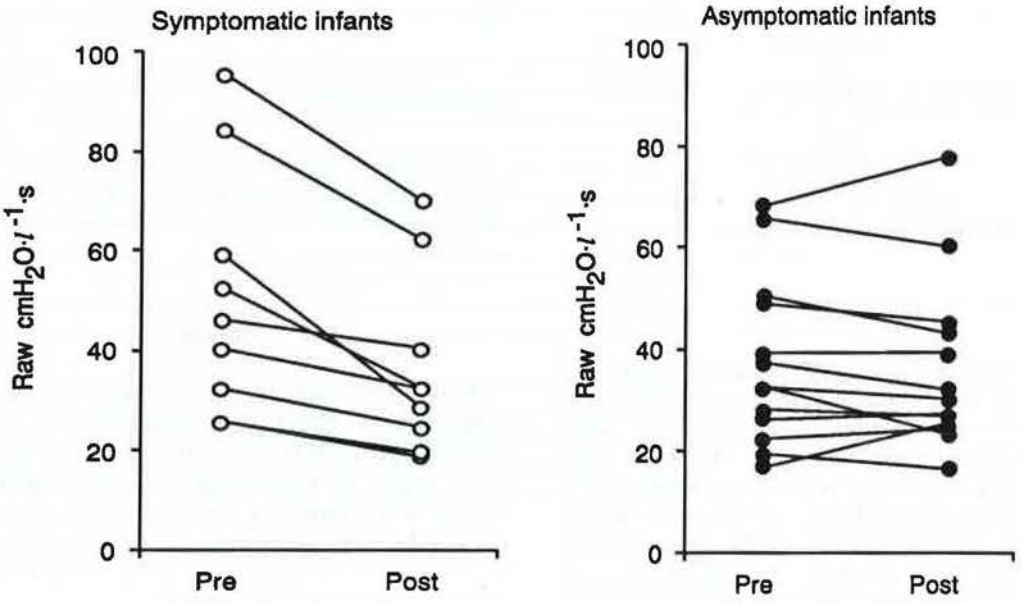

Fig. 1. – Raw before and after bronchodilator therapy in the symptomatic and asymptomatic infants. Individual data are given, each baby's results are demonstrated by linked data points. Raw: airway resistance.

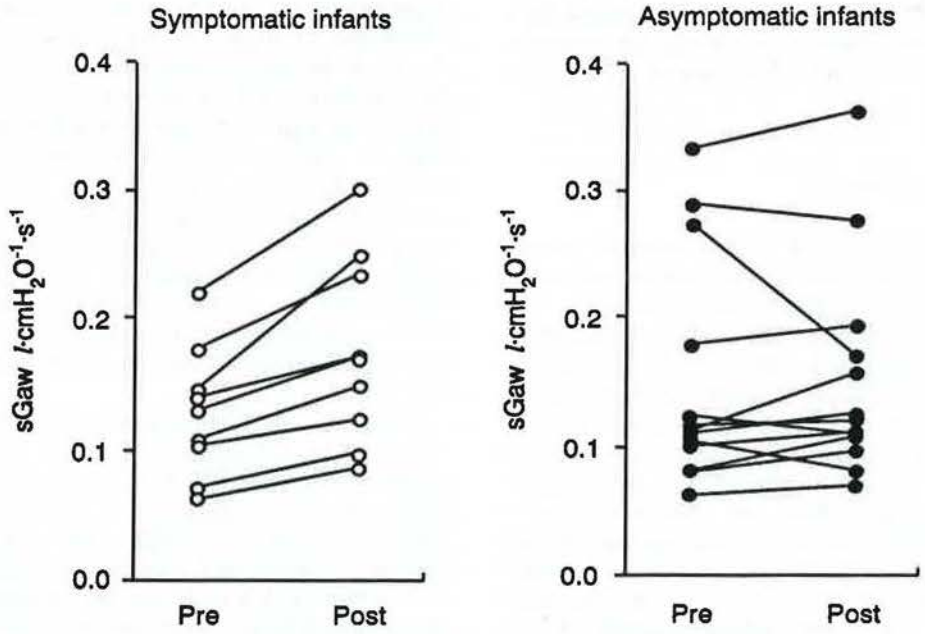

Fig. 2. – sGaw before and after bronchodilator therapy in the symptomatic and asymptomatic infants. Individual data are given, each baby's results are demonstrated by linked data points. sGaw: specific airway conductance.

Table 3. – Lung function measurements before and after normal saline

	Symptomatic infants		Asymptomatic infants	
	Pre	Post	Pre	Post
TGV $ml \cdot kg^{-1}$	33 (23.5–42.6)	32 (25–53.7)	35 (29.8–46.3)	39 (27.8–41)
Raw $cmH_2O \cdot l^{-1} \cdot s$	50 (21–90)	52 (25–95)	33 (23–68)	37 (22–68)
sGaw $cmH_2O^{-1} \cdot s^{-1}$	0.124 (0.07–0.21)	0.129 (0.06–0.22)	0.104 (0.08–0.30)	0.11 (0.08–0.28)

Data are given as mean and range in parentheses. For abbreviations see legend to table 2.

Discussion

The lung function results of the asymptomatic infants were very similar to those of preterm infants studied in our laboratory at 6 months of age, but who had had no neonatal problems or requirement for respiratory support (median TGV 36 $ml \cdot kg^{-1}$, range 25–45 $ml \cdot kg^{-1}$; median Raw 36 $cmH_2O \cdot l^{-1} \cdot s$, range 22–50 $cmH_2O \cdot l^{-1} \cdot s$) [21]. The symptomatic infants had a similar median TGV (table 2) but had a higher Raw prior to bronchodilator than our reference range [21].

These results demonstrate that salbutamol given *via* a nebulizer does provide useful bronchodilation for preterm infants in the first year of life. The improvement in lung function being greatest amongst the symptomatic infants, who had the most severe lung function abnormalities. No significant change in lung function was demonstrated following nebulized saline, emphasizing that the improvement in Raw and sGaw was a specific effect of the bronchodilator therapy.

In infants born at term a paradoxical response to salbutamol has been described, with an increase in Raw [22]. It has been suggested that this effect may be due to either the acidity or osmolality of the nebulized solution [23]. In only one infant in the present series was a statistically significant worsening of Raw noted. We studied our infants, however, 10 min after administration of the nebulized bronchodilator and Raw had almost reversed to baseline by this time in the term infants studied by O'Callaghan *et al.* [22]. Similarly, Prendeville *et al.* [24], who studied infants born at term, measured Raw approximately 15 min after administration of nebulized bronchodilator failed to detect any deterioration in Raw and indeed there was no change in Raw from baseline.

Differences in baseline lung function may explain why the beneficial effect of nebulized salbutamol was seen in the present study and not reported in the two previous trials [22, 24]. Our infants had significantly worse lung function, as evidence by an elevated Raw, than the infants included in the other two studies [22, 24]. This, however, cannot be the full explanation, as there was no significant difference between the specific conductance found in the asymptomatic and symptomatic infants in the present study, and yet a difference in response to the bronchodilator was demonstrated. Similarly, there was no apparent relationship between the magnitude of response to the bronchodilator and baseline sGaw. It should be noted, however, that the numbers of patients may be too small to demonstrate such a relationship. The other obvious difference between the three studies was that we have included only infants born very preterm and not infants born at term [22, 24]. Our results suggest that, amongst symptomatic preterm infants, salbutamol is an effective bronchodilator and this may be masking any initial bronchoconstriction effect.

We conclude that nebulized salbutamol may improve lung function in preterm infants symptomatic in the first year of life. A significant reduction in airways resistance was only seen amongst the symptomatic infants, thus it seems prudent [22] to restrict nebulized therapy to this group rather than to treat asymptomatic lung function abnormalities.

Acknowledgement: The authors thank S. Williams for secretarial support.

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Effet de la nébulisation de salbutamol chez des enfants prématurés au cours de leur première année de vie. B. Yuksel, A. Greenough.

RÉSUMÉ: Nous avons investigué l'effet aigu du salbutamol en inhalation et d'une solution placebo (solution physiologique) sur la fonction pulmonaire chez des nourrissons prématurés lors du follow-up.

Vingt-deux nourrissons prématurés, âge médian de gestation 29 semaines (extrêmes: 26–32) et poids de naissance 1.264 grammes (extrêmes: 720–1.800), ont été étudiés à un âge post-natal médian de 7 mois (extrêmes: 6–9). Neuf des nourrissons avaient des symptômes respiratoires récidivants; ils toussaient et/ou sifflaient au moins 3 jours par semaine pendant les 4 semaines précédentes. Les 13 nourrissons restants n'avaient pas de symptômes respiratoires récurrents ou persistants. Le volume des gaz intra-thoraciques et la résistance des voies aériennes ont été mesurés, et la conductance spécifique a été calculée avant et 10 minutes après l'administration par un nébuliseur, soit de salbutamol, soit de solution saline normale.

Parmi les nourrissons symptomatiques, l'administration de salbutamol en nébulisation s'est accompagnée d'une réduction médiane de 25% de la résistance des voies aériennes ($p<0.01$), ainsi que d'une amélioration significative de la conductance spécifique ($p<0.01$). Chez les enfants asymptomatiques, l'on n'a observé aucune modification significative de la résistance ni de la compliance. La nébulisation de solution saline n'a pas provoqué de modification significative de la mécanique pulmonaire dans aucun des deux groupes d'enfants.

Nous concluons que l'inhalation de salbutamol a un effet bronchodilatateur efficace chez les nourrissons prématurés symptomatiques âgés de moins d'un an.
Eur Respir J., 1991, 4, 1088–1092.