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Original

Respiratory response to salbutamol (albuterol) in ventilator-dependent infants with chronic lung disease: pressurized aerosol delivery versus intravenous injection

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Abstract. *Objective:* To compare the effects of intravenously injected with inhaled salbutamol in ventilator dependent infants with chronic lung disease (CLD).
Design: Prospective randomized study in which each patient served as his/her own control.
Setting: Multidisciplinary neonatal and pediatric ICU.
Patients: 8 ventilator dependent premature infants with CLD.
Interventions: Salbutamol, 10 µg/kg was given intravenously, and 10–19 h later, twice 100 µg as pressurized aerosol, or vice versa, sequence randomized. The pressurized aerosol was delivered by a metered dose inhaler into a newly developed aerosol holding chamber, integrated into the inspiratory limb of the patient circuit. Respiratory system mechanics were assessed by the single breath occlusion method before and 10 and 60 min after drug administration.
Measurements and results: Compliance improved significantly after intravenous injection (0.48 ± 0.18 to 0.67 ± 0.16, $p < 0.01$ and 0.59 ± 0.23 ml/cmH_2O/kg, NS, (mean ± 1 SD) and after inhalation (0.46 ± 0.19 to 0.64 ± 0.32, $p < 0.01$ and 0.56 ± 0.31 ml/cmH_2O/kg, NS). Resistance decreased after i.v. use (0.38 ± 0.17 to 0.25 ± 0.11, $p < 0.001$ and 0.25 ± 0.10 cmH_2O/ml/s, NS) and after inhalation (0.35 ± 0.12 to 0.27 ± 0.09, $p < 0.01$ and 0.28 ± 0.12 cmH_2O/ml/s, NS). Heart rate increased significantly after both routes of application, whereas mean arterial pressure, respirator settings, FIO_2, transcutaneous SO_2 and capillary PCO_2 did not change.
Conclusions: Inhaled and intravenous salbutamol improves pulmonary mechanics to the same extent with comparable side effects, and may therefore be used to facilitate weaning from respirators.

Key words: Neonate – Bronchopulmonary dysplasia – Salbutamol – Lung mechanics – Single breath occlusion method

A main component in difficulties of weaning ventilator-dependent infants with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) is increased airways resistance which may be due to bronchial smooth muscle hypertrophy and bronchospasm [1, 2]. Several authors have shown that these infants improve their bronchopulmonary status after administration of bronchodilators, delivered most often in the form of beta-2-agonists. During these studies the drug has been delivered by inhalation [2–8], subcutaneous injection [9], intravenous infusion [10] or by the oral route [11]. Most authors studying the effect of inhaled beta-2-agonists were using jet nebulization of bronchodilator solution. However, using such a system, aerosol deposition to the lungs has been found to be no more than 1–3% of the original volume of solution [12–14]. Fuller et al. have shown that by using a metered dose inhaler (MDI) and an aerosol holding chamber or "spacer", the dose deposited in the lungs can be increased 4–5 times [13]. We therefore developed a spacer for metered dose aerosol delivery, similar to those used in small asthmatic children [15]. This device can be integrated into the respiratory circuit of an infant ventilator, allowing metered pressurized aerosol delivery during uninterrupted mechanical ventilation. The aim of this study was to compare the effects of this type of beta-2-agonist delivery with the effects of intravenous injection. Changes in mechanics of the respiratory system were assessed by use of the recently introduced single breath occlusion method [16, 17].

Material and methods

Eight premature, ventilator-dependent infants fulfilling the criteria of BPD [1] were studied at a mean post-natal age of 48.1 days (range 28–70 days). Their clinical data are shown in Table 1. The study had been approved by Ethical Committee of the Department of Pediatrics, and informed consent was obtained from the parents in all cases.

Drug administration

Salbutamol (albuterol) was given intravenously and, 10–19 h (mean 16 h) apart, by inhalation or vice versa (sequence randomized, using a closed envelope system). The dose of intravenously administered salbutamol was 10 µg/kg, given as slow bolus injection of diluted solu-

Table 1. Clinical data of patients studied

Patient, Sex	Gestational age (weeks)	Birth weight (g)	Main clinical diagnosis	Postnatal age at study (days)	Body weight at study (g)	Total duration of ventilation (days)	Outcome
1, f	28	985	HMD, E. coli sepsis, PDA, BPD	28	1200	44	Survived
2, f	36	2510	Esophageal atresia, aspiration, PIE, BPD	39	3100	27	Survived
3, f	32	1730	ARDS due RSV, BPD	70	3600	14	Survived
4, m	28	1220	HMD, PDA, BPD	33	1600	56	Survived
5, m	31	1320	HMD, PDA, NEC, BPD	37	1800	49	Survived
6, m	30	1050	HMD, PDA, BPD	67	2400	127	Died (BPD)
7, f	28	810	HMD, nosocomial pneumonia, BPD	46	1600	29	Survived
8, f	29	860	HMD, pulmonary hemorrhage, PDA, BPD	65	2400	65	Survived
Mean ± 1 SD	30.3 ± 2.8	1310 ± 570		48.1 ± 16.8	2210 ± 820	51.4 ± 34.8	

ARDS, Adult respiratory distress syndrome; PDA, patent ductus arteriosus, ligated; BPD, bronchopulmonary dysplasia; HMD, hyaline membrane disease; RSV, respiratory syncytial virus; NEC, necrotizing enterocolitis; PIE, pulmonary interstitial emphysema

tion (10 μg/ml) over 5 min. (The dose of 10 μg/kg was chosen according to a protocol used in asthmatic children [18]). For inhalation 2 metered doses of pressurized salbutamol aerosol, i.e. 2 × 100 μg were puffed 5 min apart into a modified, baby adapted chamber as described by Kraemer et al. (volume of reservoir = 350 ml) [15]. The MDI was fitted into a MDI adapter (RTC 23, Instrumentation Industries Inc., Bethel Park, PA) and the spacer was integrated in the inspiratory limb of the patient circuit (Fig. 1). The puffs were given immediately prior to a mechanical breath from the ventilator (Siemens Servo 900 C, Siemens-Elema AB, Solna, Sweden; or Newport Breeze E 150, Newport Medical Instruments Inc., Newport Beach, CA). When the Newport Breeze respirator was used, the expiratory flow was set to zero in order to avoid unnecessary washout of aerosol from the spacer.

Physiological measurements

Respiratory and cardiovascular data were recorded just before, 10 min and 1 h after starting drug administration. Cardiovascular data included heart rate and blood pressure determined by the oscillometric method (Dinamap 1846 SX, Criticon GmbH, Norderstadt, Germany). Capillary blood gases (pH, PCO_2) were measured only at times 0 and 1 h, whereas transcutaneous oxygen saturation ($S_{tc}O_2$) was monitored during the whole period (Ohmeda Biox 3700 pulse oximeter, Ohmeda, Louisville, CO, USA). The mechanical properties of the respiratory system (compliance-Crs and resistance-Rrs) were assessed by the single breath occlusion method, using a Sensormedics 2600 Pediatric Pulmonary Card (Sensormedics, Yorba Linda, CA). The method has been described elsewhere in detail [16, 17], and Fig. 2 shows which linear part of the flow-volume curve was used for analysis. All patients were kept paralyzed with repeated doses of atracurium, beginning 20 min before and lasting throughout the period of physiological measurements, in order to exclude varying influences from the neuromuscular apparatus.

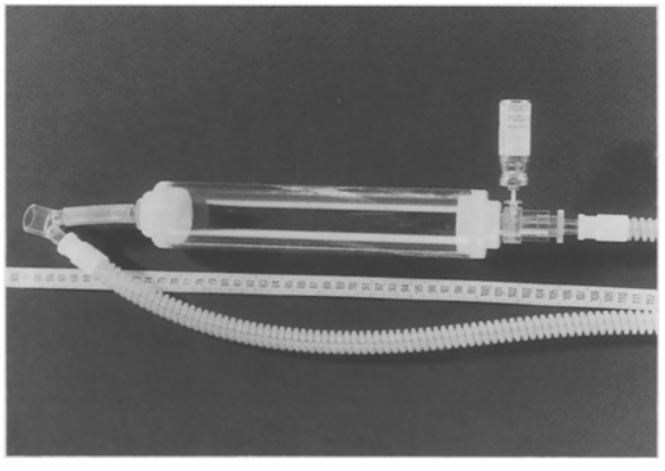

Fig. 1. Metered dose inhaler (MDI) and spacer integrated into the inspiratory limb of the patient circuit (unit of measurement = cm)

Statistical analysis

Statistical analysis was done using repeated measures analysis of variance (ANOVA) for longitudinal comparison of variables. Paired two-tailed Student's *t*-test was used for intergroup comparison (intravenous versus inhaled) of absolute values and in- or decrements at and between different time points, respectively. *P*-values < 0.05 were considered to be significant.

Results

Respirator settings were identical at the beginning of drug delivery by injection or inhalation (rate 22 ± 3 cycles/min, plateau inspiratory pressure 24 ± 2 cmH_2O, inspiratory time 0.9 ± 0.1 s, positive end-expiratory pressure 5 ± 1 cmH_2O and FIO_2 0.34 ± 0.05), and were kept unchanged throughout the study. The individual responses in lung mechanics (Crs/kg and Rrs) after i.v. and inhaled salbutamol are shown in Table 2. For illustration of the effects of salbutamol upon individual passive expiratory flow-volume characteristics, the curves of patient 6 are shown in Fig. 2.

Table 3 summarizes the data of all physiological measurements performed. Crs and Rrs improved significantly after treatment with no difference between i.v. and inhaled salbutamol, although the effect of lowering Rrs tended to be more pronounced after 60 min in the i.v. group. $P_{cap}CO_2$ tended to be lower in both groups after 60 min, however this did not reach a significant level. $S_{tc}O_2$ decreased slightly 10 min after i.v. salbutamol, but again not to a significant degree. Heart rate increased significantly in both groups, but there was no significant intergroup difference. Mean arterial pressure remained without significant changes throughout the experiment.

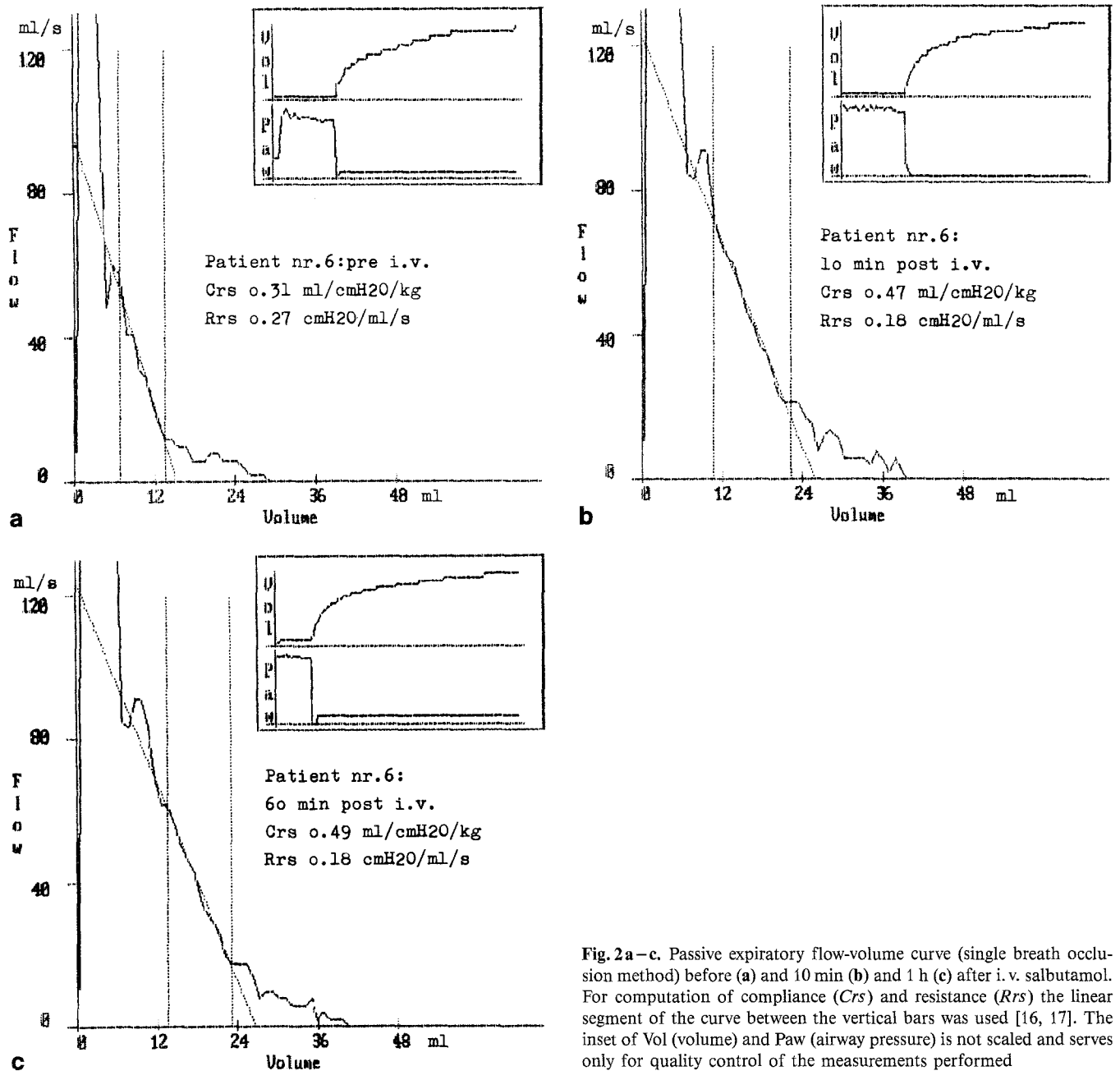

Fig. 2a–c. Passive expiratory flow-volume curve (single breath occlusion method) before (**a**) and 10 min (**b**) and 1 h (**c**) after i. v. salbutamol. For computation of compliance (*Crs*) and resistance (*Rrs*) the linear segment of the curve between the vertical bars was used [16, 17]. The inset of Vol (volume) and Paw (airway pressure) is not scaled and serves only for quality control of the measurements performed

Discussion

Our data show that in ventilator-dependent infants with CLD, intravenously injected and inhaled salbutamol acutely increased Crs and reduced Rrs. The extent of improvement of Crs and Rrs did not differ significantly between the i.v. and inhalational group. Overall, we observed an increase in Crs of 28% at 10 min after dose, and at 60 min after dose Crs was still 22% above the pre-values. This rise in Crs is most likely related to bronchodilation of small peripheral airways, resulting in recruitment of new air spaces and thus in an increased tidal volume. (The effect of volume recruitment is nicely demonstrated in Figs. 2a and 2b: with unchanged, respirator settings the expired volume increased from approximately 29 to 39 ml). The overall decrease in Rrs was 29% after 10 min and remained at 27% below pre-values 60 min after drug application. Our findings of improved Crs and Rrs are qualitatively in accordance with those of Wilkie et al. [5] and Rotschild et al. [6] who used nebulized salbutamol, Kirpalani et al. who administered the drug by infusion [10], and Denjean et al. who delivered salbutamol by MDI in a spacer, connected to a manual bag system [8]. In addition, our study demonstrates that salbutamol, delivered by metered pressurized aerosol into a spacer is effective in infants with endotracheal intubation and on mechanical ventilation. The efficacy of the same drug delivery system has recently been reported by Denjean et al. who also studied dose-related bronchodilator response (100, 200 and 400 μg) [8]. These authors used quiet sleep

Table 2. Individual responses in compliance (Crs) and resistance (Rrs) after intravenous and inhaled salbutamol

Drug delivery	Patient	Crs/kg (ml/cmH_2O/kg)			Rrs (cmH_2O/ml/s)		
		Pre-dose	10 min after dose	60 min after dose	Pre-dose	10 min after dose	60 min after dose
i.v.	1	0.68	0.88	0.93	0.29	0.28	0.20
	2	0.51	0.73	0.57	0.56	0.30	0.35
	3	0.33	0.43	0.28	0.40	0.21	0.23
	4	0.35	0.43	0.34	0.42	0.28	0.29
	5	0.38	0.43	0.55	0.67	0.47	0.41
	6	0.31	0.47	0.49	0.27	0.18	0.18
	7	0.51	0.98	0.78	0.29	0.18	0.20
	8	0.79	1.01	0.79	0.15	0.12	0.12
Inhaled	1	0.51	0.77	0.77	0.33	0.25	0.22
	2	0.34	0.48	0.41	0.40	0.29	0.26
	3	0.31	0.37	0.29	0.32	0.26	0.26
	4	0.31	0.31	0.29	0.42	0.39	0.43
	5	0.39	0.57	0.38	0.56	0.36	0.46
	6	0.33	0.41	0.38	0.38	0.25	0.28
	7	0.83	1.09	0.89	0.21	0.20	0.19
	8	0.64	1.12	1.09	0.16	0.12	0.12

states in unsedated and not paralyzed patients to carry out inhalation of salbutamol and physiological measurements; in addition the drug was delivered by manual ventilation with a bag system [8]. With the dose of 200 µg of inhaled salbutamol Denjean et al. observed a reduction of 34% of baseline Rrs, an increase of 70% of baseline Crs (single breath occlusion method), an increase of $S_{tc}O_2$ from 94–97% and an increase of heart rate from 150–180 beats/min [8]. In summary, although identical doses of inhaled salbutamol were used, the patients in Denjean's series showed a higher beta-mimetic response than our infants. This could be due to a higher amount of drug reaching the lower airways and lungs, related to the hand ventilation of the spacer or other technical, physiological or medical reasons.

With respect to gas exchange, we have been able to show that with unchanged ventilator settings and improved respiratory mechanics, $P_{cap}CO_2$ tended to be lower 60 min after salbutamol in our patients (NS). The reason for not reaching a significant level might be due to the fact that the effect of improved ventilation was offset by an increase in metabolism, i.e. CO_2-production. Newth et al. have recently been able to show that inhaled salbutamol leads to a remarkable increase in oxygen consumption in anesthetized monkeys [19]. In contrast to the results of Denjean et al. [8] we did not observe improved $S_{tc}O_2$ in our patients after salbutamol application, on the contrary $S_{tc}O_2$ tended to be lower after i.v. injection (NS). The effects of beta-agonist bronchodilators on oxygenation in patients with hyperreactive small airways and areas of atelectatic and overexpanded pulmonary parenchyma are difficult to predict: although alveolar ventilation improves, ventilation-perfusion mismatch may increase due to raised cardiac output and pulmonary vasodilation [20].

Table 3. Respiratory and cardiovascular effects of intravenous and inhaled salbutamol

		Pre-dose	*p*	10 min after dose	*p*	60 min after dose	*p* (versus pre dose)
Crs/kg (ml/cmH_2O/kg)	i.v.	0.48±0.18	<0.01	0.67±0.16	NS	0.59±0.23	NS
	Inhaled	0.46±0.19	<0.01	0.64±0.32	NS	0.56±0.31	NS
Rrs (cmH_2O/ml/s)	i.v.	0.38±0.17	<0.001	0.25±0.11	NS	0.25±0.10	<0.001
	Inhaled	0.35±0.12	<0.01	0.27±0.09	NS	0.28±0.12	<0.01
$PcapCO_2$ (mmHg)	i.v.	54±13		Not done		52±17	NS
	Inhaled	55±15		Not done		48±11	NS
$StCO_2$ (%)	i.v.	91±5	NS	89±3	NS	91±3	NS
	Inhaled	91±5	NS	92±3	NS	92±5	NS
Heart rate (beats/min)	i.v.	162±23	<0.0001	194±16	<0.01	175±18	<0.05
	Inhaled	162±15	<0.001	176±14	NS	169±16	NS
Mean arterial pressure (mmHg)	i.v.	54±13	NS	55±12	NS	52±9	NS
	Inhaled	53±12	NS	54±11	NS	59±10	NS

All intergroup (i.v. versus inhaled) differences NS

With regard to clinical application every method (i.e. jet nebulizer, MDI with a spacer and intravenous injection) has its advantages and drawbacks. Application by jet nebulizer with hand ventilation [5] is time consuming (10–15 min), an oxygen/air mixing device is required, cooling of gases might be important and there is some danger of barotrauma, unless special precautions are taken to avoid excessive pressures by hand-bagging. In addition the dose of deposited drug in the lung has been shown to be small when jet nebulizing systems are used [12, 13]. In contrast, using MDI together with a spacer spares time and allows better deposition of drug in the lungs [13]. Similar systems have been used by Grigg et al. using cromoglycate in intubated infants [14], O'Callaghan et al. who examined deposition of inhaled steroids in a rabbit model [21] and Denjean et al. who administered salbutamol in ventilator-dependent infants [8]. In addition Arnon et al. have shown in a test-lung model that the combination of MDI and spacer appears to be an extremly effective way of delivering aerosols (budenoside) to ventilated infants [22]. On the other hand the spacer is somewhat clumsy, particularly in closed incubators with limited space. In addition, if uninterrupted mechanical ventilation is desired, a respirator is needed in which the flow through the patient circuit can be set to zero during expiration in order to avoid unnecessary washout of the aerosol holding chamber. A third possibility of drug application is the intravenous injection, for which, however, venous access is needed, and systemic side effects (i.e. tachycardia) are more likely to occur (Table 3).

In conclusion we have been able to show that salbutamol 10 μg/kg by intravenous injection or twice 100 μg by MDI/spacer improves pulmonary mechanics to the same extent with comparable "costs" regarding heart rate and most likely metabolic rate. These favourable effects on Crs and Rrs might be used to facilitate weaning from the respirator. Further studies are necessary to prove relevant beneficial effects in terms of clinical management, i.e. rate of early and successful extubation in ventilator-dependent infants with CLD.

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