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Effects of inhaled formoterol compared with salbutamol in ventilated preterm infants☆

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Abstract

Background: Short-acting β_2-agonists have shown beneficial effects in preterm infants, but data on long acting β_2-agonists are still lacking.

Objectives: To compare the effects of inhaled formoterol with salbutamol in preterm infants.

Methods: Randomized, double-blind, crossover design of salbutamol (100 μg every 6 h) or formoterol (12 μg every 12 h) delivered by metered dose inhaler on two consecutive days to very low birth weight infants on assisted mechanical ventilation ($n=12$; gestational age 25.7 ± 2 weeks; birth weight 720 ± 254 g; postnatal age 25 ± 9 days; mean $\pm$ SD). Treatment with the second drug was administered until day 7 in eight infants. Outcome variables were minute volume MV, respiratory mechanics, heart rate HR, blood pressure, serum potassium and blood glucose levels.

Results: Mean MV increased by maximal 26% (salbutamol) and by 22% (formoterol) differing from baseline values until 6 and 8 h through increased mean tidal volume (V_t) in both groups (max. 14%). Mean static compliance (C_{rs}) increased by 26% (salbutamol) and by 32% (formoterol) until 60 min post-administration. There was no tachyphylaxis.

Conclusion: Inhaled salbutamol and formoterol equally increase MV, V_t, C_{rs} and HR in mechanically ventilated infants with a longer lasting systemic effect of formoterol.

Keywords: Very low birth weight; Bronchodilator; Metered dose inhaler; Albuterol; Proportional assist ventilation

1. Introduction

Beta2-receptor adrenergic or anticholinergic aerosols may be useful in relieving bronchial constriction in ventilated and non-ventilated preterm infants [1–5]. Some studies addressed this issue by comparing different modes of delivery [6–9]. Short-term benefits, mainly improved ventilation, have been shown, whereas there is no evidence for a long-term benefit—for example, a reduction in the incidence of chronic lung disease or fewer days on the ventilator [10]. The most commonly used short acting bronchodilator in preterm infants is salbutamol which however might exert systemic side effects including tachycardia, arterial hypotension, hypokalaemia and hyperglycaemia.

Formoterol, a potent selective β_2-agonist also exerts a rapid onset of action. However, it also causes a long lasting bronchodilation for at least 12 h in children with bronchial asthma [11]. In addition, anti-inflammatory effects have been reported [12]. Studies in preterm infants have not been performed so far and thus dosing and clinically relevant side

Abbreviations: VLBW infants, very low birth weight infants; GA, gestational age; MDI, metered dose inhaler; MV, minute volume; RR, respiratory rate; V_t, tidal volume; C_{rs}, static compliance; HR, heart rate; BP, blood pressure; PAV, proportional assist ventilation.

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effects [12] in preterm infants are unknown. Since a long acting β_2-agonist might have some advantages over short acting agonists in controlling poorly reversible obstructive pulmonary disease in infants, the present study is aimed at comparing the effects of formoterol with the short acting bronchodilator salbutamol in preterm infants on ventilation. Efficiency of the therapy was measured by the predefined outcome variables of minute volume (MV), respiratory rate (RR), tidal volume (V_t) and static compliance (C_{rs}), and improvement in ventilation was considered to be seen best in V_t and C_{rs}. Other outcome variables to assess potential side effects were heart rate (HR), blood pressure (BP), serum potassium and blood glucose levels. The working hypothesis was that formoterol and salbutamol evoke similar pulmonary and systemic effects, with longer duration of effect with formoterol. In addition the presence of tachyphylaxis to the drug was determined on day 7 of the study.

2. Materials and methods

The study protocol was approved by the institutional review board of the University of Munich, Germany. Written parental consent was obtained for each study participant.

2.1. Patients

Preterm infants were recruited when they met the following inclusion criteria: (1) birth weight below 1500 g; (2) postnatal age more than one week; (3) spontaneous respiratory activity; (4) requiring mechanical ventilation. If prescribed by the clinical team, theophylline therapy (3 mg/kg in four doses) was not discontinued during the study. Previous salbutamol therapy had been given if required and had been discontinued 12 h prior to the study. Infants were excluded if any of the following were present: (1) major congenital anomalies; (2) intraventricular haemorrhage higher than grade II; (3) seizures; (4) sepsis or suspected sepsis during treatment in the first 48 h; (5) patent ductus arteriosus undergoing indomethacin treatment or requiring surgical ligation; (6) elective extubation scheduled for the next two days; (7) treatment with steroids (0.3 mg/kg per day in two doses over three days) for the three days prior to this study; and (8) endotracheal tube leak of over 20% of the tidal volume, measured by the ventilator as the difference between the inspiratory and expiratory volume.

2.2. Study design and protocol

The study was double-blind, randomized, and cross-over in design. Infants received two treatments: they were randomized to either one puff salbutamol or to one puff formoterol as the initial treatment. Randomization was performed in small blocks by opaque envelopes. The assigned drug was administered every 6 h (salbutamol; 100 μg/puff) or every 12 h (formoterol; 12 μg/per puff) by MDI. Infants being assigned to formoterol received normal saline 0.9% (one puff) after 6 h. This study design was chosen to exclude sequence and carry-over effects. The clinical team and the investigator were blinded to the type of drug applied. All vials were prepared by a pharmacist who was unaware of the subsequent procedures in the study subjects. The vials were coded by the pharmacist and blinded by using an aluminium foil funnel.

Baseline recordings of MV and HR and measurements of respiratory mechanics were obtained 10 min after switching from the starting mode of ventilation (assist/control or spontaneous mandatory intermittent ventilation) to proportional assist ventilation (PAV) [13,14]. The drug was then administered and measurements were repeated at 15, 60 and 120 min, and 6 h post-administration. Between the measurements the infants were switched back to the starting ventilation mode. Ten minutes on PAV were required before each measurement was taken. The 6 h measurement constituted the baseline of the second dose (salbutamol; one puff, or normal saline 0.9%; one puff). Measurements were then repeated after the same intervals as post-administration of dose one. The last measurement on day 1 of the study was performed after 12 h. This measurement constituted the baseline of the third dose in both groups (in the formoterol group, the second dose was normal saline 0.9%). BP was measured non-invasively by the oscillometric method (Viridia CMS® Monitor, non-Invasive Blood Pressure Module, Hewlett Packard, Böblingen, Germany) after every measurement of MV, HR and respiratory mechanics. Blood gases, serum potassium and blood glucose levels were determined before measurements were started and 120 min post-administration (ABL 700®, Radiometer, Copenhagen, Denmark). All blood sampling was taken from peripheral veins by the investigator.

After the administration of four doses (four times salbutamol in one group and two times formoterol and two times NaCl 0.9% in the other group), the infants were crossed over to the alternative drug. Drug administration and all measurements were performed in the same way on the second day. Time intervals were also identical to day 1. After completion of measurements on day 2, infants were continued on the drug he/she had received after crossover for the entire week. If the infants could not be extubated until day 7 of the study, measurements were repeated on day 7 (day 6 on the same drug) before administration and 15, 60 and 120 min post-administration of dose one. Blood gases, serum potassium and blood glucose levels were determined before and 120 min post-administration of dose one.

Nursing procedures were done every 3 h and restricted to 30–40 min. The infants were placed in a supine position. The study segments were started at the same time of the day in each individual infant. Besides the two mode of assisted ventilation (assist/control or spontaneous mandatory

intermittent ventilation) during non-recording periods, there were no further differences in clinical management and timing between the treatments.

2.3. Drug dosing and drug delivery

Doses recommended for inhaled salbutamol in preterm infants with CLD are 100–200 μg/kg/dose when delivery with a MDI is chosen. Formoterol has a potency which is 5–15 times higher after inhalation than that of salbutamol, as demonstrated in adult patients with asthma [12]. Therefore, by assuming a dose equivalence to 100 μg/kg salbutamol in the medium range of formoterol potency, a formoterol dose of 12 μg/kg was chosen, which is the lowest formoterol aerosol dose on the market. We applied a uniform dose of 100 μg salbutamol (Sultanol N®, Glaxo/Wellcome/Cascan, Munich, Germany, in six patients and Salbulair N®, 3 M, Neuss, Germany, in six patients) every 6 h or 12 μg formoterol (Foradil®, Novartis, Basel, Switzerland) every 12 h. The study was performed with Sultanol N® and Foradil® in the first six infants, because formoterol was only available in a chlorofluorocarbon-pressurized preparation. The salbutamol preparation was chosen correspondingly. Starting January 1, 2001 chlorofluorocarbons were substituted by hydrofluoroalkanes in aerosols in Germany, and we therefore had to use an alternative sultanol preparation (formoterol was not available with hydrofluoroalkanes). Hydrofluoroalkane preparations are reported to have equivalent effects to chlorofluorocarbon preparations [15].

The MDI metal canister was shaken vigorously prior to actuation and was placed into the receptacle in the spacer (AeroChamber MV 15®, Trudell, Ont., Canada). Each canister was primed once or twice and the spacer was then flushed with the oxygen–air mixture of the individual infant. The MDI and spacer were placed between the endotracheal tube and an infant resuscitation bag. Manual ventilation for 20 breaths was performed by the investigator, attempting to match the ventilator inspiratory time and pressure and the breathing rate of the individual infant. FiO_2 was kept at the same level as before manual ventilation in order to avoid airway constriction in infants with chronic lung disease [16,17]. Pulse oximetry remained stable during the procedure. The infants were not submitted to suction until 1 h after treatment. A new spacer was used every day.

2.4. Ventilator settings and measurement of lung mechanics

The infants were ventilated with a Stephanie® Infant Ventilator (Stephan Biomedical, Inc., Gackenbach, Germany) and received PAV throughout the recording periods. This newer mode of assisted ventilation allows the infants to adopt their inherent breathing pattern, which varies with their activity, respiratory drive and metabolic rate [14]. During PAV the applied airway pressure increases in proportion to the instantaneous tidal volume and inspiratory airflow generated by the patient [18]. PAV was used to measure MV. This approach is described in two further studies by our group [19,20]. The end-expiratory pressure was chosen by the clinical team before the beginning of the study and was kept constant throughout the recordings. The gain of resistive unloading was set at 25 cm H_2O/l per s or at 17 cm H_2O/l per s (2.5 or 3.0 mm ID endotracheal tube) to roughly compensate for the resistance of the endotracheal tube. The elastic gain was determined individually by increasing it until elastic recoil of the lung was overcompensated and reducing it subsequently to a slightly lower level at which the infant adopted the most regular breathing pattern with appropriate tidal volumes [14]. As a safety feature backup conventional mechanical ventilation was initiated in case of apneas, but recordings were obtained only during spontaneous breathing.

Static compliance (C_{rs}) was measured by the airway occlusion technique with the Stephanie® ventilator. An automated occlusion for 200 ms of the airway at end inspiration was performed by the respirator. C_{rs} was then calculated from the occlusion plateau pressure and volume displayed at the ventilator screen. If the infants were in quiet sleep, C_{rs} was measured twice and the mean value between the two measurements was taken. If the infants had lots of active periods only one measurement was taken in order not to extend the protocol. Half of the measurements could be repeated with results close to each other.

In addition, respiratory inductive plethysmography (Respitrace Plus®, SensorMedics, Yorba Linda, CA, USA) was applied as a measurement of respiratory mechanics. Two self-adherent respiration bands were placed around the upper thorax at the level of the nipples and around the abdomen over the umbilicus. Both bands were secured in place by adhesive tape. A calibration was performed over some minutes before the start of the recordings on each day.

The paradoxical motion between rib cage and abdomen [21] is expressed by the phase shift between the rib cage and the abdominal compartment [22]. The phase shift was determined on representative breaths of each breathing pattern of the infant over the recording time. The lagtime between the onset of inspiratory motion of the rib cage compared with the abdomen was measured and expressed as a ratio of the total respiratory cycle in degrees. Perfect synchrony between the two compartments would give a value of zero, whereas fully paradox movements would give a value of 180°.

2.5. Assessment of infant behaviour

To establish an adequate sampling period without periods of vigorous activity, the infants were observed continuously and their activity was assessed on a five-point scale adapted from Brück [23]. Behaviour was coded as follows: 0, quiet sleep, no movements; 1, active asleep, occasional movements; 2, quiet awake, occasional movements; 3, active awake, body movements; 4, vigorous activity, such as kicking and crying. Moderate, not

continuously occurring movements were tolerated during the recording periods, but periods of arousal and excitement without movements were not. Recordings were interrupted when scale values of 3 and 4 were reached or when arousal or excitement without movement was observed. Behaviour scoring served only to interrupt the recordings during periods of continuous and vigorous activity and was only then noted in the protocol.

2.6. Data processing and analysis/statistics

Airflow and airway pressure were obtained from the analogue outlets of the ventilator. HR was obtained from the monitor (Viridia CMS®, Hewlett Packard, Böblingen, Germany). Plethysmographic signals from both respiration bands were directly obtained from the Respitrace Plus®. All signals were digitized at a rate of 100 Hz and recorded on disk over 10 min using data acquisition software (Windaq Pro+®, Dataq Instruments, Inc., Akron, OH).

The recorded plethysmographic signals were evaluated manually before, 60 and 120 min after the first dose taking into account the assessment of paradoxic motion between rib cage and abdomen [21,24]. Data analysis of MV, V_t, RR and HR was done after all recordings of the 12 infants had been obtained by computer programs (Windaq Playback®, Dataq Instruments, Inc., Akron, OH and Labdat system®, Nelson Claure, Miami, FL). This study design provided two sets of data for salbutamol and for formoterol (first and second dose) for each infant (except plethysmography). An extra set of data for salbutamol and formoterol (first dose) was available for infants still intubated and ventilated on day 7 of the study. Variables before the administration of the first dose (baseline values) were compared with those after administration of the first dose, before and after the second dose, before the third dose and before and after any further doses on the following day by repeated measurements ANOVA and post hoc paired *t*-tests, if a difference was found between groups. Comparisons between the two drugs were made using paired *t*-tests. Testing for normality was performed before all statistical tests. For discrete variables (RR), ANOVA on ranks and Wilcoxon tests were performed. Statistical significance was defined as $p<0.05$. All data are reported as mean±SD.

3. Results

Of the 16 infants who met the entry criteria during the time the study was performed four infants were not enrolled for the following reasons: two were not entered because the parents refused their consent and two were not studied because of absence of the investigator in the unit at the time of enrollment. Twelve infants were studied, five boys and seven girls (Table 1). All infants were oxygen dependent and could not be extubated at the time of inclusion in the study or had already experienced extubation failure.

Table 1
Demographic characteristics of 12 infants studied

	Mean±SD	Range
Gestational age (weeks)	25.7±2.1	23.1–29.4
Birth weight (g)	720±254	490–1085
Postnatal age (days)	25±9	13–40
Body weight at study (g)	960±257	707–1520
FiO_2	0.46±0.12	0.3–0.7
Days on the ventilator	23±9	13–40
	n	%
Surfactant treatment	12	100
On theophylline	5	42
Previous dexamethasone therapy	6	50
Previous salbutamol therapy	2	17

During PAV all infants had pCO_2 values in the range of 61±5.9 mm Hg.

Mean MV increased from 364 ml/kg per min (baseline) to a maximum level of 489 ml/kg per min (26%) when salbutamol was administered, and to a maximum level of 464 ml/kg per min (22%) when formoterol was administered (Fig. 1). Values differed up to 6 h from baseline levels

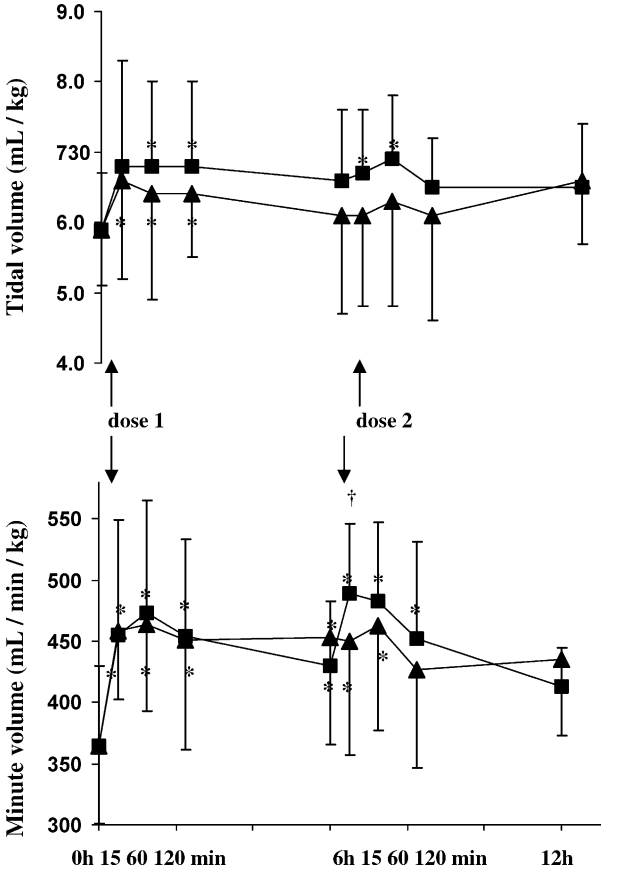

Fig. 1. Minute volume (ml/min per kg) and tidal volume (ml/kg) in the salbutamol group (■) and in the formoterol group (▲) in 12 infants. *$p<0.05$, compared to baseline value †$p<0.05$, compared between the variables in the salbutamol and the formoterol group.

in the salbutamol group (the drug was then administered again) and up to 8 h in the formoterol group. Baseline values after 12 h still showed a trend towards higher levels ($p=0.06$ and 0.09). The increase in MV was mainly due to an increase in V_t (maximum difference to baseline levels 14%) (Fig. 1), although there was also a trend to an increase in RR (Fig. 2). Formoterol showed a trend to cause a smaller increase in V_t, but a higher increase in RR than salbutamol. C_{rs} increased by 32% (formoterol) and by 26% (salbutamol) after treatment. C_{rs} values differed to baseline levels 15 and 60 min post-administration (Fig. 3). HR increased by 5% in the formoterol group and by 7% in the salbutamol group and the duration of the increase was 12 and 2 h, respectively (Fig. 2). There was no difference in mean BP (34–41 ± 3–8 mm Hg), venous pCO_2 (60–65 ± 7–8 mm Hg) serum potassium (4.0–4.3 ± 0.5–0.7 mmol/l) and blood glucose levels (123–158 ± 39–88 mg/dl) before and after the administration of the drug. Respiratory inductive plethysmography recordings could be obtained on eight infants in the formoterol group and on six infants in the salbutamol group. Four out of 12 infants had no plethysmography (no parental consent or unavailability of the device). Bronchodilator treatment reduced asynchrony and paradoxic chest wall movement in four of six infants in

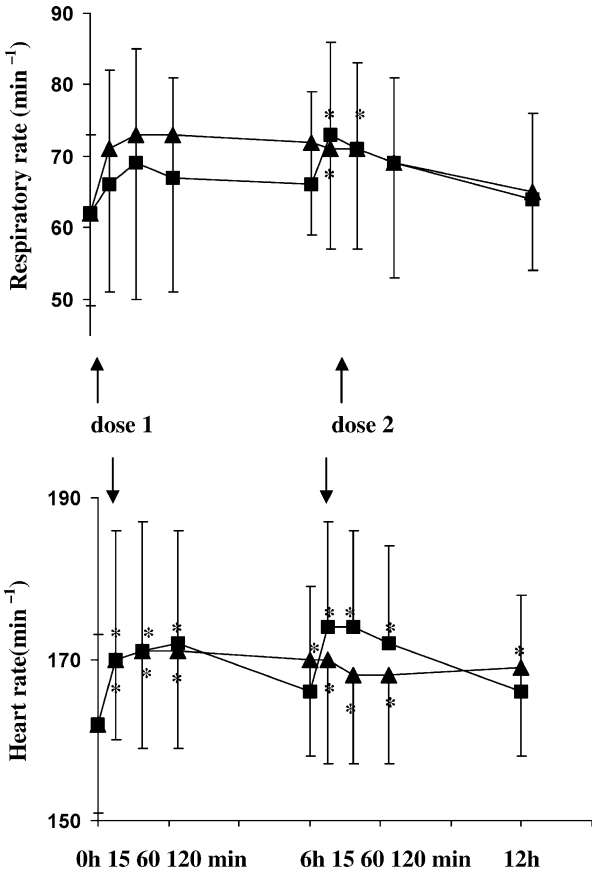

Fig. 2. Heart rate/min and respiratory rate/min in the salbutamol group (■) and in the formoterol group (▲) in 12 infants. *$p<0.05$, compared to baseline values.

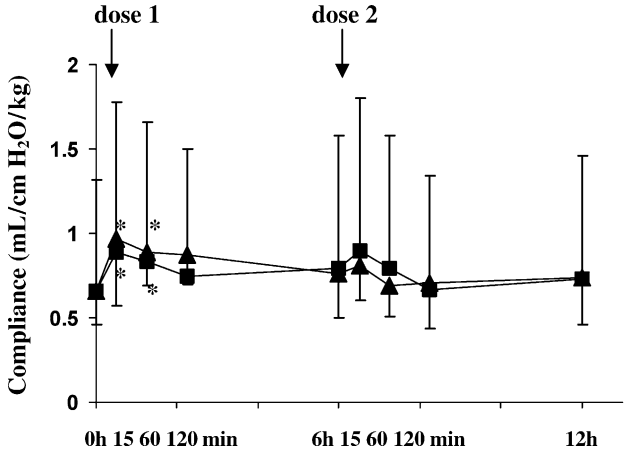

Fig. 3. Compliance values (ml/cm H_2O/kg) in the salbutamol group (■) and in the formoterol group (▲) in 12 infants. *$p<0.05$, compared to baseline values.

the salbutamol group ($p>0.05$) (in three infants after 1 h, in one infant after 2 h) and in seven of eight infants in the formoterol group ($p=0.057$) 1 and 2 h after treatment (Fig. 4). Four infants with large swings in phase shift (two in each group) dominate. Phase shift was 77° before treatment, 45° after 1 h and 69° after 2 h in the salbutamol group, and 91°–56°–59° in the formoterol group (mean values). The differences were not statistically significant, most likely because of the small sample size (Fig. 4). The only statistically significant difference between the formoterol and the salbutamol group was: MV was higher 15 min after the 6 h dose in the salbutamol group, when normal saline 0.9% had been given in the formoterol group (Fig. 1).

On day 7 eight infants were still intubated. Measurements could be performed on five infants in the salbutamol group, and on three infants in the formoterol group. No statistical analyses were performed on these data because of the small sample size in each group. MV and HR increased in the same range or to slightly lower levels; compliance remained at higher levels after one week on bronchodilator

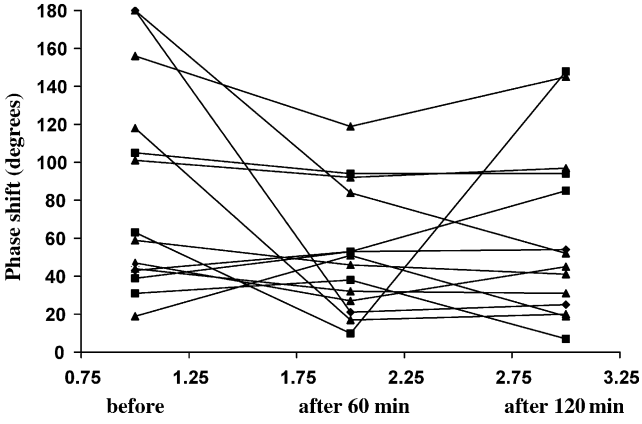

Fig. 4. Phase shift between rib cage and abdomen in degrees in six infants in the salbutamol group (■) and in eight infants in the formoterol group (▲) before and after treatment.

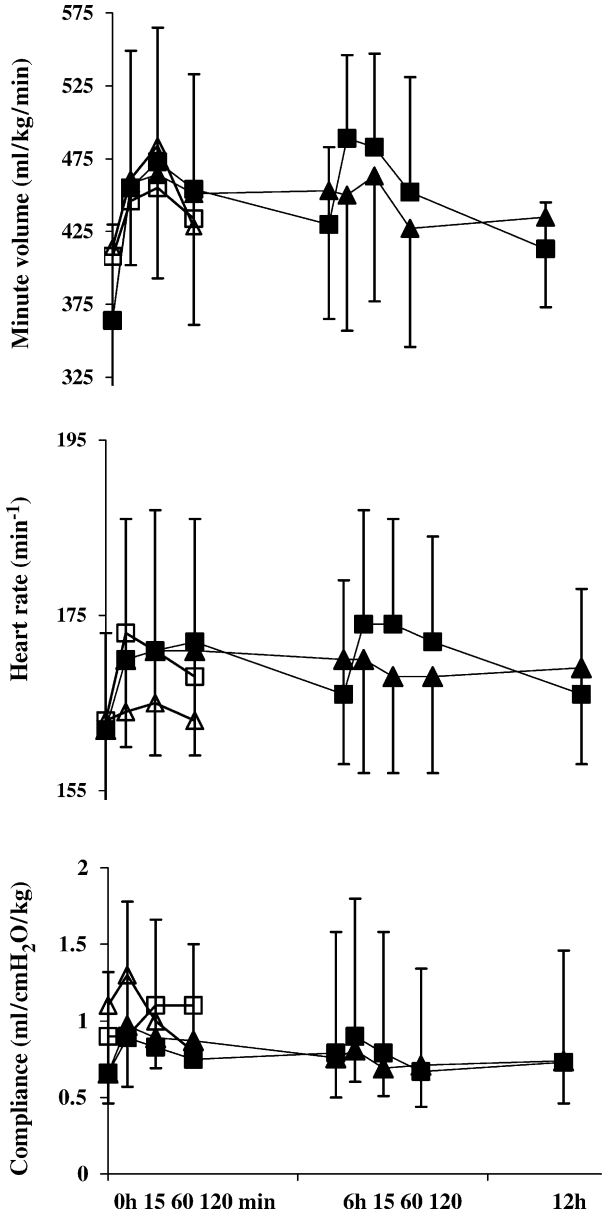

Fig. 5. Minute volume (ml/min per kg), heart rate (min^{-1}) and compliance (ml/cm H_2O/kg) on days 1 and 2 in 12 infants (thick lines) and on day 7 (thin lines) in eight infants on salbutamol (■, □) and on formoterol (▲, △).

treatment (Fig. 5), indicating no tachyphylaxis in this small group.

4. Discussion

This study shows that inhaled formoterol increases MV and HR to a similar extent as salbutamol and produces similar improvements of lung mechanics in preterm infants, but the systemic effects of formoterol were more consistent. Twelve micrograms of formoterol twice daily seem to be equivalent to 100 μg salbutamol four times daily delivered by MDI. There were no obvious differences in effects between the two drugs. No tachyphylaxis occurred after one week on bronchodilator treatment.

β_2-sympathomimetic agonists are widely used for relief of asthmatic attacks and/or as add on drugs to glucocorticoids in the long-term treatment of bronchial asthma in adults as well as in children. In extremely preterm infants with and without lung disease, there is sufficient bronchial smooth muscle to respond to inhaled bronchodilators as early as 25 weeks of gestational age and 7 days of life [25]. However, data of aerosolised bronchodilators in ventilated neonates and preterm infants are less consistent than in older children suffering from asthma. One reason for that might be the smaller deposition of the drug molecules within the lower airways because of a loss to the ventilator circuit and the endotracheal tube [26]. However, recent data gave clear cut evidence that the delivery of short acting β_2-agonists within the lung was greatest using a MDI and a spacer [5,15]. This study uses, for the first time, the short-term β_2-agonist salbutamol and the selective long acting β_2-agonist formoterol; both drugs applied by a MDI. In addition, in order to improve the efficacy of the device, we also placed the spacer between the endotracheal tube and a resuscitation bag, i.e. not into the inspiratory limb of the circuit. Although an exact estimation of the drug deposition in preterm infants is not available from the literature, we used 100 μg salbutamol which was administered by four individual puffs within 24 h according to data from Ref. [2]. Since data of formoterol in ventilated preterm infants are lacking so far, we adapted dosages from asthmatic adults [11] which have shown a dose equivalence of 100 μg/kg salbutamol applied four times per 24 h with 12 μg/kg formoterol applied every 12 h. According to the data presented, the deposition rate was high enough to show an improvement of MV, V_t, and C_{rs} as well as an increase of HR.

The present study was performed in a small population of preterm infants. Sample size was not calculated a priori, because the variance of the data was not known. Few studies have measured MV after the administration of bronchodilators in ventilated subjects [27], none of them in ventilated infants treated with salbutamol. We performed a cross-over trial in 12 infants to assess the treatment effects of both drugs in this population, and found significant differences to baseline values for MV, V_t, RR and C_{rs}. This study has a power of 90% to detect differences in minute ventilation and even higher to detect changes in HR. The power to detect differences in other outcome variables such as tidal volume and lung compliance is lower (16 and 60%, respectively) due to the small sample size and the high variability of the data. The findings of this small study therefore need to be further validated.

A limitation of the chosen study design is that the duration of the salbutamol effects could not be exactly determined, because an effect duration in MV and HR could still be found 6 h after application of salbutamol. Thus it appears that the duration of action as was estimated by

Wilkie et al. [4] in ventilated neonates can be extended in preterm infants. The effect duration of formoterol in our study is in line with data reported in children [12].

We measured MV in VLBW infants undergoing PAV, a mode that allows unrestricted control of all variables of the ventilatory pattern by the infant. We therefore assume that the recorded breathing pattern represents the infants' endogenous respiratory drive. PAV was used only during the measurement of MV (including 10 min to adapt to PAV) and does therefore not limit the generalizability of these data.

We do not believe that blood gases are a reliable outcome variable in this study for the following reasons. The infants had two different starting modes of ventilation (assist/control or spontaneous mandatory intermittent ventilation). Blood gases were taken before the administration of the drug and after 2 h when the infants had been switched to PAV for the recording and measuring periods, which varied in time according to the infants' behaviour (measurements were only taken during quiet periods). Different time spans on PAV (15–30 min) and on two different modes of ventilation between the recordings might have influenced the pCO_2 values.

MV and V_t increased after application of either salbutamol or formoterol. It is assumed that the increase of MV and V_t might be due to the bronchodilating effects of both drugs. However, MV might be influenced also by RR, which increased slightly and was not significantly different from baseline values presumably because of the small sample size.

As shown by other authors, we also found an increase in static compliance measured by the occlusion technique. Both, the short and the long acting β-agonist showed a similar duration of effect on C_{rs}. It is believed that this was due to a reopening of smaller airways being involved in the elastic properties of the lungs in this age group and to a recruitment of atelectatic alveoli [1,4,5]. However, the improved lung function could also be due to a fluid shift from the alveoli to the interstitial compartment in the lung [28,29].

Due to a stimulation of cardiac β_1-adrenoreceptors [27], formoterol increased the HR to a similar extent as salbutamol, but we did not find a decreased BP as was reported in healthy adult volunteers and adult patients with asthma [11].

It would appear from the data that the dominant response has been systemic. The increases in HR, RR and MV are almost identically matched in timing. V_t and C_{rs} increased rapidly after the administration of the drug, returning to levels around baseline values within 120 min. Our data demonstrate a longer lasting systemic effect of formoterol than of salbutamol, but no difference in improvement in lung function as measured by C_{rs} after 120 min.

Hypokalaemia and hyperglycaemia are reported side effects of both drugs [11], but did not occur in normokalaemic and normoglycaemic infants in our study. In one infant, an already low serum potassium baseline level of 3.4 mmol/l potassium decreased to 2.6 mmol/l 120 min after treatment with salbutamol. The infant was asymptomatic and normal values were achieved after intravenous potassium substitution over one day.

As to the onset and the maximum of effect achieved by salbutamol and formoterol there occurred no significant differences between the two drugs in our study. Small differences, however, might have been masked by a type II error.

It remains unclear what proportion of the observed improvement in ventilation after one week which lead to extubation in four infants was due to the inhaled bronchodilators or to clinical improvement over time.

Although we did not find adverse drug effects in the study population except one case of hypokalaemia after salbutamol, the sample size was too small to determine such effects. Therefore, we cannot give any final conclusion about the safety of formoterol in preterm infants, but it appears from our data that, within the dose range chosen, formoterol might be safe.

In conclusion formoterol improved lung mechanics and led to a similar change of respiratory pattern and HR as salbutamol. We showed that the systemic effect of 12 μg/kg formoterol was present up to 8–12 h after drug administration and was more consistent than that of salbutamol. However, we could not find a longer lasting improvement in lung function as measured by C_{rs} than with salbutamol. The drug is well tolerated by children above the age of 6 years [12] and showed no side effects in our study. However, more research concerning treatment safety in preterm infants is required, before the administration of formoterol can be recommended in this group of patients.

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