Albuterol Delivery During Noninvasive Ventilation

Matthew P Branconnier RRT and Dean R Hess PhD RRT FAARC

HYPOTHESIS: Albuterol delivered during noninvasive positive-pressure ventilation is affected by use of a nebulizer or metered-dose inhaler (MDI) and whether the leak port is in the hose or the mask. METHODS: A lung model that simulated spontaneous breathing at 20 breaths/min was used. A bi-level positive-airway-pressure ventilator (Respironics S/T30) was set for an inspiratory positive airway pressure of 15 cm H_2O and an expiratory positive airway pressure of 5 cm H_2O. The tidal volume delivered was 0.4 L. Two mask types were used: one in which the leak port was incorporated into the circuit, and another in which the leak port was incorporated into the mask. The nebulizer was filled with 4 mL, which contained 5 mg of albuterol, connected via a T-piece directly to the mask, and operated at 8 L/min for 15 min. For the MDI studies, a spacer was placed between the mask and the circuit, and an MDI was actuated into the spacer, either synchronized with the initiation of inhalation or during the exhalation phase (4 actuations separated by ≥ 15 s in each case). Albuterol was washed from the filter and measured with ultraviolet spectrophotometry. RESULTS: With the nebulizer, significantly more albuterol was delivered to the filter when the leak port was in the circuit ($p = 0.001$). Significantly more albuterol was delivered with the nebulizer than with the MDI ($p < 0.001$). The efficiency of albuterol delivery (percent delivered) was similar for nebulizer and MDI with the leak port in the circuit ($p = 0.57$), but better with the MDI with the leak port in the mask ($p = 0.001$). Albuterol delivery was significantly less when the MDI was actuated during exhalation ($p = 0.001$). CONCLUSIONS: Albuterol delivery with noninvasive positive-pressure ventilation was affected by the type of aerosol delivery device, by the location of the leak port, and by actuating the MDI at the proper time in the respiratory cycle. *Key words: chronic obstructive pulmonary disease, mask ventilation, metered-dose inhaler, nebulizer, noninvasive positive-pressure ventilation.* [Respir Care 2005;50(12):1649–1653. © 2005 Daedalus Enterprises]

Introduction

Much evidence supports the use of noninvasive positive-pressure ventilation (NPPV), and arguably the best evidence is from patients with chronic obstructive pulmonary disease exacerbation.[1] These patients also benefit from the administration of inhaled bronchodilators. Despite a large volume of published work related to aerosol delivery to intubated mechanically ventilated patients,[2] surprisingly little has been published related to aerosol delivery during NPPV. Anecdotally, we have seen a variety of approaches to this therapy, with no clear standard practice.

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To our knowledge, there have only been 4 papers[3–6] published to date on this topic, including the use of a nebulizer with NPPV in patients with asthma,[3] use of a breath-actuated nebulizer with NPPV in children with cystic fibrosis,[4] use of a metered-dose inhaler (MDI) and spacer with NPPV in patients with chronic obstructive

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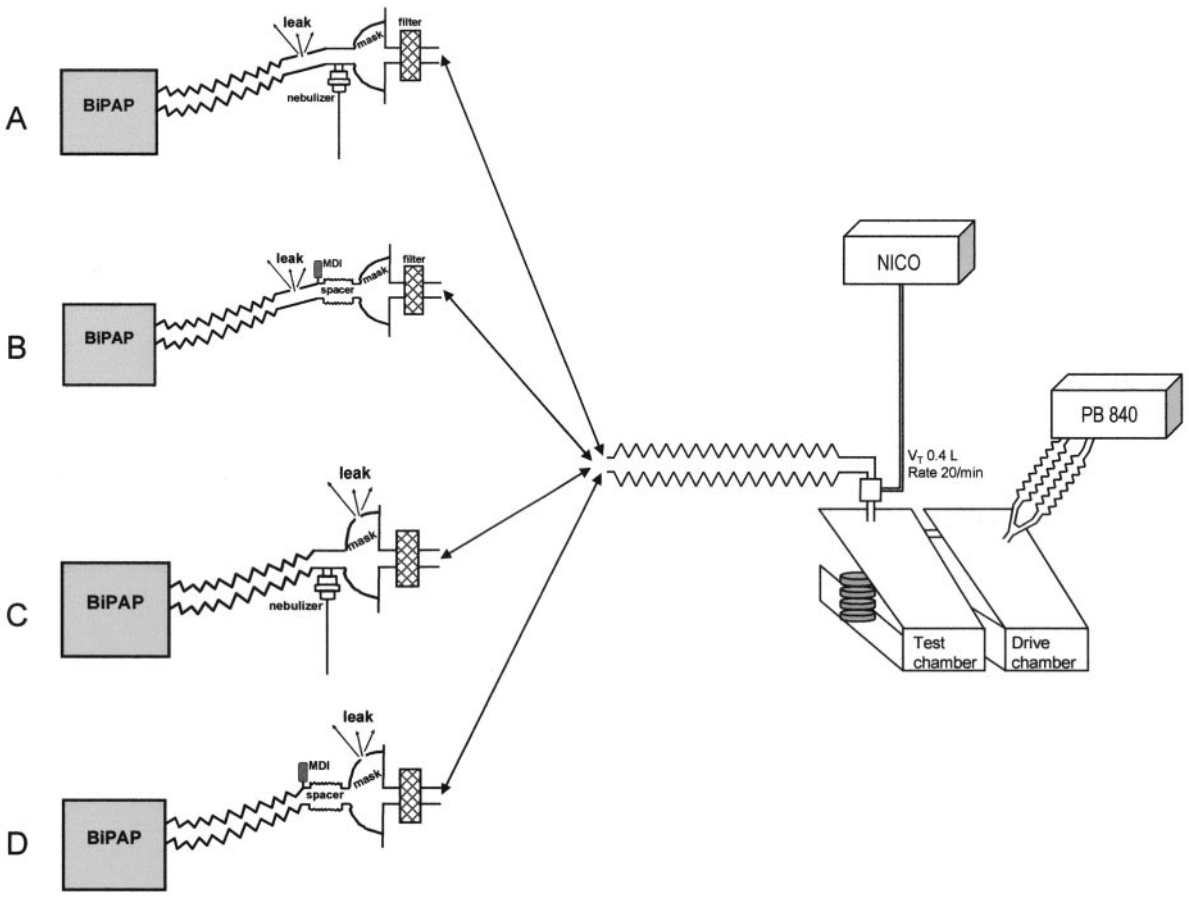

Fig. 1. Experimental setup. A: Spectrum mask with nebulizer. B: Spectrum mask with metered-dose inhaler (MDI) and spacer. C: Mirage mask with nebulizer. D: Mirage mask with MDI and spacer. BiPAP = bi-level positive airway pressure. NICO = Respironics NICO cardiopulmonary monitor. PB840 = Puritan Bennett 840 ventilator.

pulmonary disease,[5] and an in vitro evaluation of aerosol delivery with a nebulizer during NPPV.[6] We designed this in vitro study using a lung model and filter deposition to evaluate the effect of leak port position and aerosol delivery device on albuterol delivery during NPPV. Our hypothesis was that albuterol delivery during NPPV is affected by use of nebulizer versus MDI and whether the leak port is in the hose or mask.

Methods

Experimental Model

A ventilator (model 840, Puritan-Bennett, Carlsbad, California) was attached to one chamber of a dual-chambered test lung (Michigan Instruments, Grand Rapids, Michigan) (Fig. 1). A lift bar placed between the chambers simulated spontaneous breathing in the second chamber, at 20 breaths/min. A bi-level positive-airway-pressure ventilator (BiPAP S/T30, Respironics, Murrysville, Pennsylvania) was set for an inspiratory positive airway pressure of 15 cm H_2O and an expiratory positive airway pressure of 5 cm H_2O. The compliance of the lung model was adjusted to achieve a tidal volume of 0.4 L measured with a cardiorespiratory monitor (NICO, Respironics, Murrysville, Pennsylvania). A single-limb circuit was placed between the BiPAP ventilator and an oronasal mask. The mask was glued to a Plexiglas plate and a 15-mm connection led to an absolute filter (D/Flex, Puritan-Bennett, Carlsbad, California) and the test lung.

Experimental Conditions

The Spectrum mask (Respironics, Murrysville, Pennsylvania) has the leak port in the circuit, whereas the Mirage mask (ResMed, Poway, California) has the leak port in the mask. For the nebulizer experiments, a nebulizer (Micro Mist, Hudson RCI, Temecula, California) was connected via a T-piece directly to the mask. With the Spectrum mask, the nebulizer was placed between the mask and the leak port. The nebulizer was filled with 4 mL, which contained 5 mg of albuterol, and operated at 8 L/min for 15

min, using a calibrated flow meter (Timemeter, St Louis, Missouri). For the MDI studies, a spacer (AeroVent, Monaghan, Plattsburgh, New York) was placed between the mask and the BiPAP circuit. An MDI (100 μg of albuterol from the valve per actuation) (albuterol inhalation aerosol, Warrick Pharmaceuticals, Reno Nevada) was actuated into the spacer, either synchronized with the initiation of inhalation or during the expiratory phase (4 actuations separated by $\geq$ 15 s in each case). Data were collected in triplicate.

Albuterol Measurement

For the nebulizer experiments, 20 mL of 0.9% saline solution was used to wash the aerosol collected on the filter. The filter was shaken for 1 min to ensure proper mixing, using a mixer (model 16700, Thermolyne, Dubuque, Iowa). The light absorption of the solution washed from the filter was measured with a spectrophotometer (DU Series 500, Beckman Instruments, Fullerton, California) using a 1-mL quartz cuvette at a wavelength of 276 nm. The amount of albuterol captured on the filter was calculated from the absorption-concentration standard curve generated by plotting light absorption as a function of albuterol concentration. There was a linear relationship between absorption and concentration of albuterol between 0 and 0.05 mg/mL, with a slope of 0.1426 ($r^2 = 0.99$).

For the MDI experiments, the filter was washed with 0.1 M NaOH and analyzed at 243 nm. The standard curve for these experiments was linear between 0 and 100 μg/mL, with a slope of 0.0323 ($r^2 = 0.99$).

We tested the filter's ability to trap aerosol by placing 2 filters in series, and no albuterol was detected on the second filter. We also tested the specificity of our analytic technique by nebulization of saline, with which we found no absorption. A known amount of albuterol was mixed in the filter with saline to determine whether all the albuterol was recovered, and all the albuterol was detected.

Statistical Analysis

The amount of delivered albuterol was expressed in absolute terms and as a percentage of the nominal dose. The nominal dose for the nebulizer was the dose placed into the nebulizer cup (5 mg). The nominal dose for the MDI was 400 μg (100 μg/puff for 4 puffs). For both the nebulizer and the MDI experiments, albuterol delivery for the 2 masks was compared using univariate analysis of variance. All statistical analysis was performed using commercially available software (SPSS version 11.5, SPSS, Chicago, Illinois). Differences were considered statistically significant when $p < 0.05$.

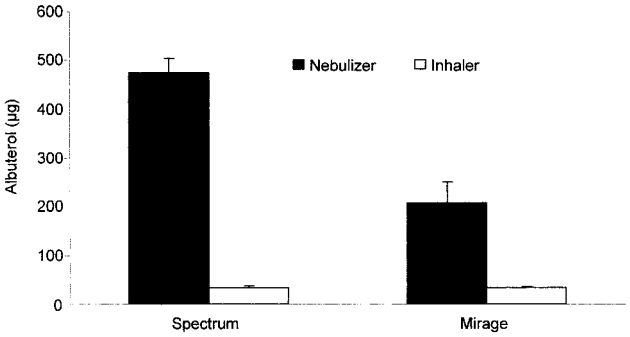

Fig. 2. Absolute amount of albuterol delivered with nebulizer and metered-dose inhaler with the Spectrum and Mirage masks. The Spectrum mask incorporates the leak port into the circuit, whereas the Mirage mask incorporates the leak port into the mask.

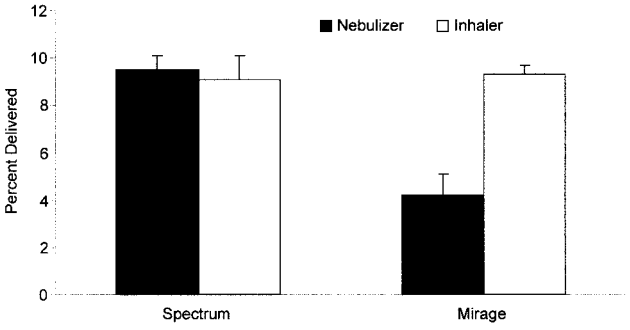

Fig. 3. Percent of the nominal dose of albuterol delivered with nebulizer and metered-dose inhaler with the Spectrum and Mirage masks. The Spectrum mask incorporates the leak port into the circuit, whereas the Mirage mask incorporates the leak port into the mask.

Results

With the nebulizer, significantly more albuterol was delivered to the filter with the Spectrum mask ($p = 0.001$), and significantly more albuterol was delivered with the nebulizer than with the MDI ($p < 0.001$) (Fig. 2). The amount of albuterol delivered with the MDI was similar for the Spectrum and the Mirage masks ($p = 0.71$). The efficiency of albuterol delivery (percent delivered) was similar for the nebulizer and the MDI with the Spectrum mask ($p = 0.57$), but better for the MDI with the Mirage mask ($p < 0.001$) (Fig. 3). Albuterol delivery was significantly less when the MDI was actuated during exhalation ($p < 0.001$) (Fig. 4).

Discussion

The major findings of this study are: (1) during NPPV using a ventilator with a leak port, more aerosolized bronchodilator was delivered when the leak port was in the circuit rather than the mask; (2) the efficiency of the MDI

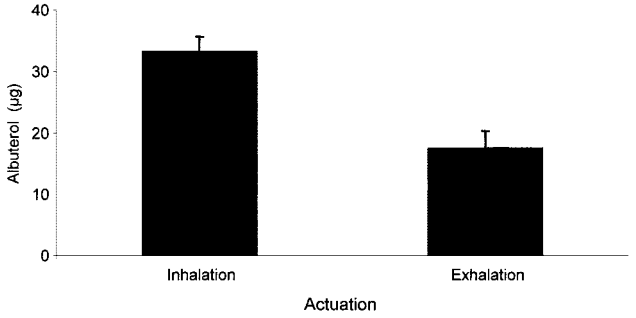

Fig. 4. Absolute amount of albuterol delivered when the metered-dose inhaler was actuated at the initiation of inhalation, compared to actuation during exhalation. The nominal dose of albuterol was 400 μg (4 actuations).

with spacer was similar to the nebulizer when the leak port was in the circuit, but the efficiency was greater with the MDI when the leak port was in the mask; and (3) aerosolized bronchodilator delivery was significantly reduced when the MDI was actuated during the expiratory phase.

In a previous study we reported that the optimum nebulizer position during NPPV is between the leak port and the mask.[6] In the study by Pollack et al,[3] the nebulizer was incorporated between the leak port and the mask. Accordingly, when we incorporated the use of the Mirage mask into our practice we were concerned about how this would affect aerosol delivery. Indeed, we found that aerosol delivery was reduced by more that 50% when the nebulizer was used with the Mirage mask rather than the Spectrum mask. Presumably this relates to greater aerosol waste through the leak port into the mask. This suggests that the nebulizer dose may need to be increased if the leak port is in the mask. Fauroux et al[4] reported that aerosol deposition can be significantly enhanced when combined with the use of noninvasive pressure-support ventilation. That study, however, differed from ours, because they used a home-care ventilator that does not incorporate a leak port in the circuit, and the nebulizer was active only during the inspiratory phase.

To our knowledge, there is only one published study that evaluated the use of MDI during NPPV.[5] In that study, a home-care ventilator was used with volume-assured pressure support mode. In the United States, a ventilator with a leak port is more commonly used with NPPV. Therefore, it is of interest to characterize aerosol delivery via MDI using such a ventilator system. Our data suggest that an MDI can be used efficiently during NPPV with a ventilator that has a leak port. Moreover, the efficiency is similar whether the leak port is incorporated into the circuit or into the mask. However, the delivered dose is significantly reduced if the MDI is actuated during the expiratory phase. With invasive ventilation, Diot et al[7] also reported the importance of actuating the MDI with the initiation of the inspiratory phase.

Although the efficiency of the MDI is similar to that of the nebulizer, the absolute dose is greater with the nebulizer. This is related to the higher nominal dose with the nebulizer (5 mg), compared to that with 4 MDI actuations (0.4 mg). Despite the lower delivered dose with MDI, a clinically important response has been demonstrated during both noninvasive[5] and invasive ventilation.[8] The similar efficiency of the nebulizer and MDI reported in our study suggests that the MDI might be used effectively with many patients receiving NPPV. If a high dose is needed, either a nebulizer can be used or the number of MDI actuations can be increased. Moreover, our results suggest that the delivered dose with the MDI is relatively consistent, regardless of the position of the leak port. In fact, with the Mirage mask the MDI delivered a more efficient dose than the nebulizer.

Our results suggest that the nebulizer dose may need to be increased with a system that incorporates the leak port into the mask. A measurable amount of albuterol is delivered if an MDI with spacer is used, and, moreover, the delivered dose is relatively constant, regardless of the position of the leak port. Our results suggest that an MDI can be used during NPPV, but it is important that it is actuated at the initiation of the inspiratory phase.

Our in vitro data should be confirmed clinically. Extrapolating in vitro results can be problematic unless key variables are carefully controlled.[9] We compared only 2 types of leak ports, and care must be used if extrapolating these results to other types of leak ports that may be used during NPPV. We used only one type of spacer with the MDI, and one type of nebulizer, and we evaluated only one drug formulation. We used only one brand of ventilator, 2 mask types, one nebulizer position in the circuit, and one ventilatory pattern. Further work should evaluate the effect of these factors on aerosol delivery during NPPV.

We used both mask types with the same ventilator, although that ventilator was specifically designed for the mask that has the leak port in the circuit. In our practice, masks and ventilators are commonly interchanged, and, to our knowledge, this has not been reported to affect ventilator function. One study[10] reported the dynamic dead space in masks used for NPPV. That study compared various combinations of masks and ventilators and did not report interference with ventilator function. In a previous study from our laboratory,[11] we reported oxygen delivery using different masks with the same ventilator type and reported no interference with ventilator function. In this study we detected no obvious interference with ventilator function using the different mask types.

Conclusions

Albuterol delivery with NPPV is affected by the aerosol delivery device, by the location of the leak port, and by

actuating the MDI at the proper time in the respiratory cycle.

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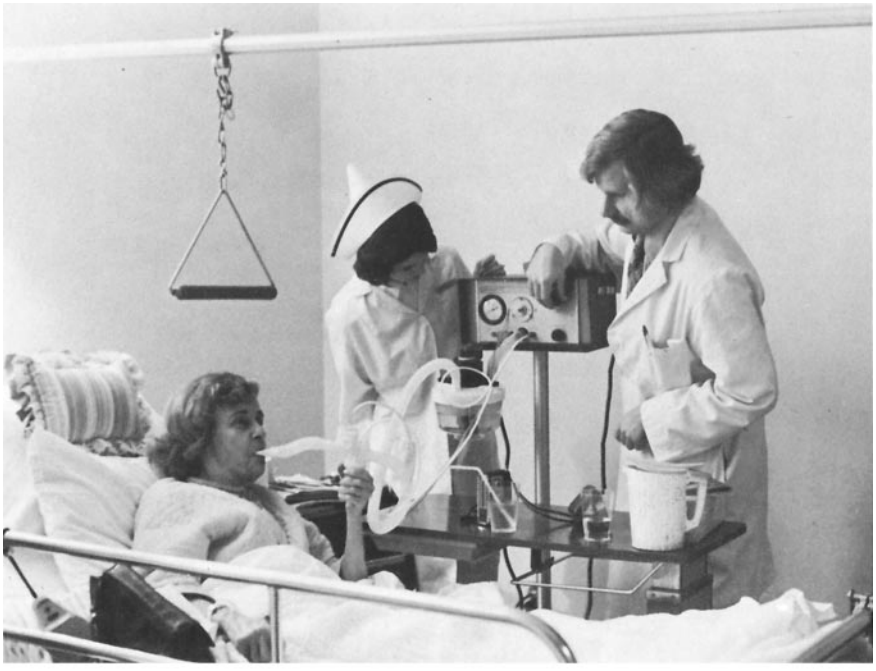

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