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Efficiency of Different Aerosol Devices and Masks during Noninvasive Positive Pressure Ventilation in a Simulated Adult Lung Model

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Abstract

Introduction: The aim of this study was to evaluate the efficiency of aerosol devices in a simulated adult lung model using different NIV masks.

Methods: A ventilator with NIV circuit was attached via face mask to a manikin with a collecting filter at the level of the bronchi attached to a passive test lung. Aerosol devices: (1) Jet Nebulizer (JN); (2) Vibrating Mesh Nebulizer (VMN) and (3) Pressurized metered-dose inhaler (pMDI), were placed between the leak port and mask. NIV with PIP/PEEP of 20/5 cmH2O was used with full face mask, oro-nasal mask, and Performa track mask (Philips, Murrysville, PA). Albuterol sulfate (2.5 mg/3 ml) was nebulized with JN and VMN. Fourpuffs from a pMDI (108 µg/puff) were emitted into a spacer (Aerovent, Monaghan/Trudell) in recommended and reverse orientation (n=3). Drug was eluted from filters and analyzed by UV/Spec at 276 nm. Inhaled mass and percent of nominal/emitted dose were quantified. Descriptive statistics, Kruskal Wallis analysis of variance, and Mann-Whitney U tests were used for data analysis.

Results: During NIV, inhaled mass percent ranged from 13.12% ± 0.72% to 28.83% ± 1.93% across devices. VMN had greater inhaled mass than JN (p=0.0001). Efficiency of pMDI was similar with both orientations (p=0.253). Both Solo and NIVO were more efficient with oro-nasal mask than full face mask (p=0.012 and p=0.037, respectively.)

Conclusion: The efficiency of aerosol devices and masks during NIV varied in this simulated adult lung model. The JN was less efficient than either VMN or pMDI with spacer.

Keywords: Noninvasive positive pressure ventilation; Aerosols; Inhalation devices; Metered dose inhalers; Nebulizers and vaporizers; Vibrating mesh nebulizer

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Introduction

Clinically, noninvasive ventilation (NIV) has been utilized to decrease the need for endotracheal intubation, ultimately, decreasing the length of stay and improve mortality rate [1]. Many patients who require NIV suffer from airflow limitation. Although aerosol drug delivery during NIV is commonly utilized in the treatment of critically ill patients, only seven *in vitro* [2-8] studies were found in the literature about their simultaneous use. More research is needed to understand the efficiency of aerosol devices in conjunction with NIV. The findings of previous studies suggest that NIV settings, type of aerosol device, timing of actuation, location of aerosol device, location of exhalation port, and type of exhalation port could affect aerosol deposition. However, research thus far has not determined which type of aerosol device and mask combination should be used to optimize aerosol drug delivery in patients receiving NIV. Additionally, there is no study in the literature that has compared the jet nebulizer (JN), the pressurized metered-dose inhaler (pMDI) and the vibrating mesh nebulizer (VMN) on aerosol drug delivery during NIV. Only three studies used a NIV mask as an interface with a simulated lung with airway in their models [3,7,8]. The type of mask used during NIV can alter patient comfort, tolerance and ventilation. We hypothesized that delivery efficiency of aerosol devices and masks vary during NIV. The aim of this study was to evaluate the efficiency of JN, pMDI and VMNs in a simulated adult lung model using different NIV masks available on the market.

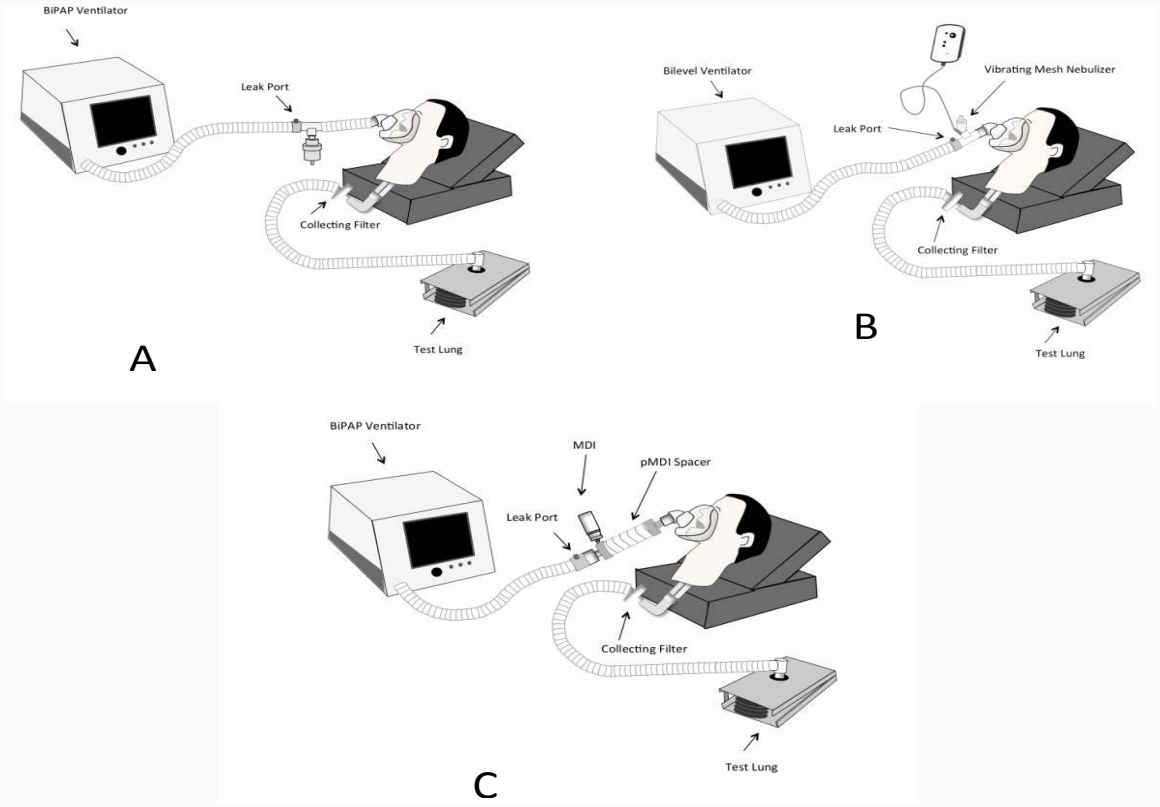

Figure 1: Experimental set-up of the study using the jet nebulizer (A) and the vibrating mesh nebulizer (B) and the pressurized metered-dose inhaler (pMDI) (C).

Materials and Methods

Lung model

An *in vitro* lung model consisted of a teaching mannequin with an upper airway that was attached to a collecting filter at the level of the bronchi, which was connected to a passive single chamber test lung (QuickLung, IngMar Medical, Pittsburgh, USA) with settings for airway resistance (Raw) = 5 cmH_2O/L/sec and compliance (C_L)=20 mL/cmH_2O. Our target tidal volume was 450 mL, which is reasonable for an adult male receiving NIV. The tidal volume ranged from 433 mL to 477 mL. The leak was monitored continuously during experiments and ranged from 4% to 17% in this study.

A noninvasive ventilator (BiPAP® Vision®, Respironics, Murrysville, PA) with a single limb NIV circuit (Philips, Respironics, PA) was attached to each facemask tested in this study. Face masks were securely attached to the head of the teaching manikin to minimize leak. The ventilator was set on the spontaneous/time mode with a respiratory rate of 15 BPM and an inspiratory time of 1.0 second, with pressure settings of IPAP/ EPAP 20/5 cmH_2O. In this study, we did not provide heated humidification and room temperature was 25°C ± 2°C with relative humidity of 40% to 60%. Figure 1 represents experimental set-up of the study using the jet nebulizer (Figure 1A) and the vibrating mesh nebulizer (Figure 1B) and the pressurized metered-dose inhaler (pMDI) (Figure 1C).

Comparisons of Aerosol Devices and NIV Masks

Experiment 1: Types and operation of aerosol devices

Three types of aerosol devices were investigated in this study:

- JN (Micro Mist, Hudson RCI, Temecula, CA) was operated with 8 L/min of oxygen to nebulize albuterol sulfate (2.5 mg/3 mL) until sputter.
- pMDI (Pro Air HFA, Teva Specialty Pharmaceuticals, Atlanta, GA) with a spacer (Aero Vent, Monaghan/Trudell Medical, Plattsburgh, New York). The pMDI was shaken and primed, then connected to the NIV circuit through the spacer, which was connected either as recommended on the label (actuator distal and emitting aerosol towards the patient) or in reversed positions. The pMDI actuation was synchronized with the beginning of the inspiratory cycle for a total of four actuations (108 µg emitted/puff).
- Vibrating mesh nebulizer (VMN) (Aeroneb Solo, Aerogen Ltd, Galway, Ireland) was operated continuously to nebulize albuterol sulfate (2.5 mg/3 mL) until no more aerosol was produced.

Each aerosol device was placed between the face mask (Oro-nasal mask, Respironics, Inc., Murrysville, PA) and the fixed orifice leak port on the circuit. The residual volume of each nebulizer was measured with the gravimetric method only in experiment 1 testing different nebulizers used during NIV.

Experiment 2: Comparisons of NIVM asks with VMNs

Two types of VMNs were used in the comparisons of three NIV masks: (1) Aerogen Solo (Aerogen, Galway, Ireland) and (2) NIVO (Phillips Respironics, Carlsbad, CA). Aerogen Solo is designed to be used in spontaneous breathing patients, ventilator-dependent patients and patients receiving NIV. However, NIVO is specifically designed for aerosol drug delivery during NIV. Each VMN was placed between the leak port and the mask and operated until the end of nebulization.

As shown in Figure 2, three types of masks used in this study

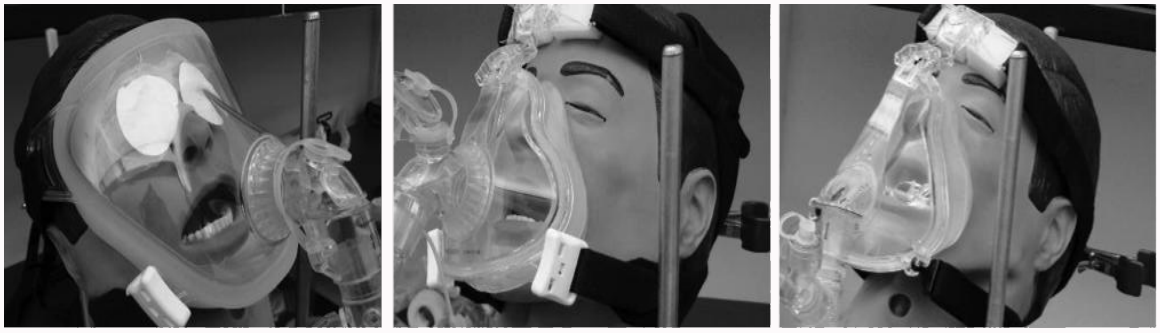

Figure 2: Three interfaces tested from left to right, full face mask, oronasal mask, and Performa track mask.

Table 1: Inhaled mass (mg), inhaled mass percent (%), and residual volume (g) obtained with the jet nebulizer (JN), the vibrating mesh nebulizer (VMN), pressurized metered dose inhaler (pMDI) with spacer in normal/recommended (pMDI-N) or reversed position (pMDI-R).

Aerosol Devices	JN	VMN	pMDI-N	pMDI-R
Inhaled Mass (mg)	0.33 ± 0.02	0.72 ± 0.05	0.10 ± 0.01	0.09 ± 0.01
Inhaled Mass Percent (%)	13.12 ± 0.72	28.83 ± 1.93	23.53 ± 2.03	21.38 ± 0.32
Residual volume (g)	1.65 ± 0.14	0.10 ± 0.07		

include: 1) Full face mask (Performax mask, Respironics, Inc., Murrysville, PA), 2)Oro-nasal mask (AF531, Respironics, Inc., Murrysville, PA), and 3) Performa Track mask (Respironics, Inc., Murrysville, PA). The full face mask and the oro-nasal mask were investigated with both the Aerogen Solo and NIVO. The Performa track mask was only tested with the Aerogen Solo due to the inability to connect with the NIVO. We included the full-face mask so that we could compare inhaled dose with each device/mask combination and quantify drug deposited on filters placed over the eyes of the manikin.

Measurement of Aerosol Deposition

An absolute collecting filter (Respirgard II, 303, Vital Signs, Totowa, NY) was attached to the bronchi of the manikin. In addition, glass filter discs (EMD Millipore, Billerica, Massachusetts, USA) were placed over the eyes of the manikin when using the full-face mask. After the completion of each experiment, each collecting filter was eluted with 10 mL of 0.1 N HCl and shaken for three minutes. The concentration of albuterol from the filter was measured via a spectrophotometer (Beckman Instruments, Fullerton, CA) at 276 nm. Each experiment was repeated in triplicate (n=3).

Data Analysis

Albuterol deposition was quantified and reported as inhaled mass and a percentage of the nominal dose placed in the reservoir of the nebulizer or label dose of drug emitted from the pMDI. Data was analyzed with the Statistical Package for the Social Sciences (IBM SPSS, 18.0, Armonk, NY). Means and standard deviations were calculated for the three devices. A one-way analysis of variance (ANOVA) was used not only to compare the means of aerosol deposition obtained from the three aerosol devices tested in this study but also to compare inhaled mass and inhaled mass % of the three different masks used with Aerogen Solo only. An independent t-test was used to compare residual volume in the VMN and the JN. A significance level of 0.05 was used for all comparisons.

Results

Table 1 shows the mean and standard deviation (SD) for inhaled mass and percentage of nominal dose delivered with each aerosol device and residual volume of nebulizers. During NIV, inhaled mass and inhaled mass percent obtained with each aerosol device vary significantly ($p=0.042$ and $p=0.028$, respectively). While VMN is the most efficient aerosol device in this simulated adult lung model receiving NIV, the findings of this study showed that aerosol delivery with JN is the lowest compared to other aerosol devices tested in this study. No significant difference was found between VMN and pMDI ($p=0.109$). Delivery efficiency of pMDI was not significantly different at both positions ($p=0.253$). In addition, the residual volume of the VMN was significantly lower than the JN ($p=0.0001$). While the mean residual volume of the VMN was 0.10 ml, it was 1.65 ml with the JN.

Table 2 shows the mean and SD values for inhaled mass and percentage of nominal dose obtained with each aerosol device/mask combination. The findings of this study showed that aerosol delivery obtained with the three masks and the two VMNs varied significantly ($p<0.05$) during NIV. With both VMN (Aerogen Solo and NIVO), delivery efficiency of the oro-nasal mask was greater than the full face mask ($p=0.012$ and $p=0.037$, respectively). Aerosol drug delivery with these nebulizers was similar with the full-face mask ($p=0.284$). The drug eluted from the filters placed over the eyes during aerosol therapy with the full-face mask was below detectable limits. All other comparisons were not statistically significant.

Discussion

This study showed that the type of aerosol device used during NIV influenced aerosol delivery in this simulated adult lung model. The JN was less efficient than the VMN and the pMDI in either orientation during NIV. Aerosol delivery with the oro-nasal mask using the Aerogen Solo was more than the other masks tested in this simulated adult lung model receiving NIV. The findings of this study showed that eye exposure with the full-face mask was below the limits of detection in our method, suggesting less than 1% of dose would contact the eyes with this mask.

There are a total of eight clinical studies in the literature testing aerosol drug delivery to normal subjects and patients with asthma or COPD receiving NIV [9-16]. Chatmongkolchart et al. [4] and Dai et al. [5] compared aerosol delivery in different BiPAP settings. Both

Table 2: Inhaled mass (mg) and inhaled mass percent (%) obtained with the full face mask, the oro-nasal mask and the Performa Track mask using NIVO and the Aerogen Solo.

Nebulizers	NIVO		Aerogen Solo		
Masks	**Full-face Mask**	**Oro-nasal Mask**	**Full-face Mask**	**Oro-nasal Mask**	**Performa Track Mask**
Inhaled Mass (mg)	0.49 ± 0.02	0.58 ± 0.02	0.53 ± 0.04	0.72 ± 0.05	0.46 ± 0.06
Inhaled mass percent (%)	19.59 ± 1.05	23.07 ± 0.70	21.02 ± 1.93	28.83 ± 1.93	18.51 ± 2.47

studies reported a direct relation between delta pressures and aerosol deposition during NIV. In our study, when different aerosol devices and masks were tested in a simulated adult lung model, the inhaled mass varied between 0.09 mg and 0.72 mg, representing 13% to 29% of the emitted or nominal dose. Using the oro-nasal mask, the inhaled mass with VMN was approximately two-fold greater than JN, and seven-fold greater than pMDI (in either orientation). These findings are consistent with those of Ari et al. [16] when comparing VMN, pMDI and JN in a model of conventional mechanical ventilation.

Abdelrahim et al. [2] reported an inhaled mass percent of 51% with a VMN (Aerogen Pro, Aerogen Ltd, Galway, Ireland) placed between the fixed orifice and a collecting filter placed before the test lung. The differences in the findings of this study from our research can be explained with the lung model used in this study. We used an anatomically representative upper airway and collected inhaled aerosols distal to the bronchi. The passage of aerosol through the upper airways results in impactive losses of aerosol droplet, reducing the dose delivered distal to the upper airway. Consequently, our model measuring aerosol deposited distal to the trachea provides a more realistic estimation dose available to the lung.

Michotte et al. [6] reported similar aerosol deposition with NIVO, Aerogen Pro and Aerogen Solo using similar conditions. Branconnier and Hess [3] utilized a more realistic model with an actual non-invasive mask. The findings of their study showed a better aerosol deposition with the spectrum mask, which had a leak port at the circuit when compared with the mirage mask that has a leak port at the mask; however, the inhaled mass % with the spectrum mask was about 9% for JN and 8.5% for the pMDI.

Chatmongkolchart et al. [4] reported approximately 25% delivery efficiency with JN. Although the same brand of JN was used in our study, aerosol deposition obtained with JN in our study was approximately 13%. Differences in our results are due to breathing parameters and lung models that were utilized. For example, Chatmongkolchart et al. [4] used higher respiratory rate (20 breath/min) compared to our study (15 breath/min). Also, they did not utilize a noninvasive mask in their model and the inspiratory filter was connected directly to the circuit unlike our study.

White et al. [7] have utilized a pediatric model with simulating an asthma attack and the highest inhaled mass % was 11% when using NIVO. Clearly, the patient status and breathing pattern can alter aerosol delivery and resulted in a reduction of more than 50% compared to our findings in which we used a simulated adult lung model receiving NIV.

Galindo-Filho et al. [17] administered radio labeled aerosol via JN and NIVO to 10 healthy subjects during NIV with 12/5 cmH_2O using the oronasal face mask. They reported an inhaled dose of 23.1% with the NIVO, which was similar to the result of our study with an inhaled mass of 23.07% using same mask but different parameters. In contrast, inhaled dose with JN was lower at 6.1% in vivo versus 13.12% in our model. This may be a result of different nebulizers, ventilator parameters spontaneous breathing patients versus a passive test lung used in these studies. Our study used S/T mode with IPAP/EPAP of 20/5 cmH_2O and RR 15 breath/min with no spontaneous effort. Those fixed settings may not mimic the clinical dynamic situation for a patient with airway limitation. However, these parameters are similar to the previous *in vitro* studies [2,7,8].

The pMDI spacer has 22 mm male fittings to connect to tubing, and a 22 mm female fitting attached to the "y" of a standard two limb vent circuit. The pMDI was placed in the port proximal to the 22 mm male fitting, and aerosol plume was emitted towards the patient. With the single limb circuit to mask, adapters are required at both ends of the spacer to place in the manufacturer recommended "ventilator" orientation. Because the fittings on the spacer fit without adapter when the orientation is reversed we were curious how much the orientation mattered. Our data suggests that dose delivered was similar with recommended and reversed positions.

Concerns have been raised about ocular deposition of aerosol when delivering aerosol with mask interfaces. We wanted to quantify drug delivered to the eye with the full-face mask. As the drug eluted from the filters were below detectable limits, we conclude that drug exposure to the eyes during mask administration was minimal in our model.

Limitations of the Study

The ventilator used in this study is no longer manufactured, but is still in clinical use for acute and chronic conditions with ventilator settings that have been used in four published *in vitro* aerosol studies [2-5]. Additionally, the settings of NIV we used (20/5 cmH_2O) were also utilized in two studies that reported high inhaled mass or inhaled mass % [2,8]. Therefore, the mode of bilevel ventilation and parameters used in our study are consistent with those available in the newer bilevel ventilators. More importantly the ventilator provided consistent ventilation of the model across testing with the different aerosol generators.

Our model of active ventilation may yield different results than the same ventilator parameters assisting spontaneous ventilation. However, prior comparisons of aerosol delivery during controlled and assisted ventilation have shown similar comparative efficiency of the devices used. Our study only utilized one set of adult ventilator parameters to provide a consistent point of comparison of aerosol devices and masks tested in this study. Future studies should explore the impact of a broader range of parameters with both controlled and assisted ventilation.

This was an *in vitro* study and thus results could differ when reproduced in an *in vivo* setting with considerable biological variability; however, our findings can serve as a guide for clinical research and can be used to support clinical management strategies.

Conclusion

In conclusion, the findings of this study showed that VMN was

the most efficient aerosol generator with the lowest residual volume. However, pMDI could be an attractive alternative to VMN since it provides a similar aerosol deposition. The oro-nasal mask with the Aerogen Solo provided the highest drug deposition and may be consider as a first option for aerosol therapy during NIV. Other masks did not differ statistically. Therefore, the mask selection should be based on patient's need and comfort level, and availability.

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