The Effect of Using Different Aerosol Devices and Masks on Aerosol Deposition during Noninvasive Positive Pressure Ventilation in an Adult Lung Model

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This thesis, THE EFFECT OF AEROSOL DEVICES AND MASKS ON AEROSOL DEPOSITION DURING NONINVASIVE POSITIVE PRESSURE VENTILATION IN AN ADULT LUNG MODEL, by Maher M. AlQuaimi was prepared under the direction of the Master’s Thesis Advisory Committee of the Respiratory Therapy department at Georgia State University. It is accepted by the committee in partial fulfillment of requirements for the Master’s of Science degree in Respiratory Therapy at Byrdine F. Lewis School of Nursing and Health Professions, Georgia State University. The Master’s Thesis Advisory Committee, as representatives of the faculty, certifies that this thesis has met all standards of excellence and scholarship as determined by the faculty.

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ABSTRACT

Introduction: Although patients with an acute increase in airflow resistance may require aerosol therapy and noninvasive positive pressure ventilation (NIPPV), the efficiency of different aerosol devices and masks during NIPPV is not well understood. The purpose of this study was to determine the efficiency of a jet nebulizer (JN), a vibrating mesh nebulizer (VMN) and a pressurized metered-dose inhaler (pMDI) and three different masks during NIPPV.

Method: An in vitro lung model consisted of the upper airway of an adult teaching manikin with a collecting filter at the level of the bronchi attached to a passive test lung. NIPPV was administered via full face mask for the first experiment (AF531 oro-nasal) with an IPAP/EPAP of 20/5 cm H2O and a respiratory rate of 15 Breath per minute (BPM). Aerosol generators were placed between the leak in the circuit and the mask. Albuterol sulfate (2.5 mg/3 ml) was nebulized with the JN (Micromist) and the VMN (AeronebSolo). Four puffs (108 µg/puff) were administered with the pMDI (ProAir HFA) with a spacer (Aerovent) that first was placed in the recommended normal position (pMDI-N) with aerosol plume directed towards patient, and then in the reversed position (pMDI-R), with aerosol directed away from patient (n=3). In the second experiment, three masks were used 1) the Performax mask, 2) the AF531 oro-nasal mask, and 3) the Performa track mask. Performa track mask was tested with only Aeroneb solo while other masks were tested with both Aeroneb solo and NIVO VMNs. In both experiments, filters were eluted with 0.1 HCl and analyzed by a spectrophotometer at 276 nm. Residual volumes were determined gravimetrically.
**Result:** Descriptive statistics, one-way analysis of variance (ANOVA), and independent t-tests were used. Statistical significance was set at $p<0.05$. During NIPPV, inhaled mass (IM) and inhaled mass percent (IM %) varied significantly ($p=0.042$ and $p=0.028$, respectively). Aerosol delivery with the JN was the lowest during NIPPV. The VMN has a significantly lower residual volume than the JN ($p=0.0001$). No statistical difference in efficiency was found between the two pMDI orientations ($p=0.253$). In the second experiment, oro nasal mask with Aeroneb Solo VMN results in the highest IM which was significant when compared with all other masks ($p=0.0001$). No statistical difference can be found between other masks.

**Conclusion:** The JN was less efficient than the VMN and the pMDI in either orientation. The type of aerosol device used during NIPPV influenced aerosol delivery in this simulated adult lung model. Oro nasal mask with Aeroneb Solo VMN provided the highest IM.
THE EFFECT OF USING DIFFERENT AEROSOL DEVICES AND MASKS ON AEROSOL DEPOSITION DURING NONINVASIVE POSITIVE PRESSURE VENTILATION IN AN ADULT LUNG MODEL

By
Maher M. AlQuaimi

A Thesis
Presented in Partial Fulfillment of Requirements for the Degree of Masters of Science in Health Sciences in the Division of Respiratory Therapy in Byrdine F. Lewis School of Nursing and Health Professions Georgia State University Atlanta, Georgia 2011
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>BiPAP</td>
<td>bilevel positive airway pressure</td>
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<td>BPM</td>
<td>breaths per minute</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<td>expiratory positive airway pressure</td>
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<tr>
<td>FEF_{25%-75%}</td>
<td>forced expiratory flow between 25 and 75%</td>
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<tr>
<td>FiO$_2$</td>
<td>fraction of inspired oxygen</td>
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<td>FVC</td>
<td>forced vital capacity</td>
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<tr>
<td>JN</td>
<td>Jet nebulizer</td>
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<tr>
<td>HFA</td>
<td>hydrofluoroalkane</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<td>IM</td>
<td>inhaled mass</td>
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<tr>
<td>IM%</td>
<td>inhaled mass percentage</td>
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<tr>
<td>IPAP</td>
<td>inspiratory positive airway pressure</td>
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<tr>
<td>IPPB</td>
<td>intermittent positive pressure breathing</td>
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<tr>
<td>LPM</td>
<td>liters per minute</td>
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<tr>
<td>MMAD</td>
<td>mass median aerosol diameter</td>
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<tr>
<td>NIPPV</td>
<td>noninvasive positive pressure ventilation</td>
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<td>PaO$_2$</td>
<td>arterial oxygen partial pressure</td>
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SVN    small volume nebulizer
VMN    vibrating mesh nebulizer
CHAPTER I
INTRODUCTION

Noninvasive positive pressure ventilation (NIPPV) can be delivered to a patient with an intact airway through a face mask or similar interface (Crummy & Naughton, 2007). By leaving the upper airway intact, NIPPV preserves airway defense mechanisms, and patients are able to eat and drink, speak, cough and expectorate secretions, and avoid specific complications associated with an endotracheal tube, such as ventilator-associated pneumonia, sinusitis, and tracheal stenosis (Crummy & Naughton, 2007). In addition, patients may not need to be on sedatives, analgesics, or paralytics to start or maintain NIPPV. In a 2003 meta-analysis involving eight studies with more than 600 patients, Lightowler and his colleagues showed that the use of NIPPV resulted in a highly significant reduction in mortality rate (relative risk 41%) and the need for intubation (relative risk 42%). They concluded that NIPPV is an effective intervention in the management of acute respiratory failure secondary to acute hypercapnic exacerbations of chronic obstructive pulmonary disease (COPD).

NIPPV is a very cost-effective intervention, avoiding intubation and intensive care unit (ICU) admission, without prolonging hospital length of stay (Plant, Owen, Parrott, & Elliott, 2003). It also can be used safely on the general ward (Al-Mutairi & Al-Deen, 2004; Crummy & Naughton, 2007), which could avoid the need for ICU admission. Plant, Owen, Parrott, and Elliott (2003) have suggested that treatment with NIPPV may avoid between three and nine ICU admissions per year in a regional UK general hospital, resulting in a potential annual cost saving of up to £53 000 (US$125,000).
During NIPPV, alveolar ventilation is improved by the application of positive pressure through a nasal mask, oral mask, face mask, full face mask, or hamlet, thereby avoiding the need for an endotracheal or tracheostomy tube to perform invasive ventilation. Inhaled aerosol therapy has gained widespread acceptance because of its advantages over other alternative routes for drug administration (Ari, Hess, Myers, & Rau, 2009).

A “medical aerosol” is any suspension of liquid (nebulizer or pressurized metered-dose inhaler [pMDI]) or solid drug particles (pMDI or dry powder inhaler) in a carrier gas (Ari et al., 2009). Aerosol delivered through the inhalation route has been used widely to treat different diseases such as COPD, asthma, cystic fibrosis, and pneumonia. It has advantages over the systematic route, such as the ability to use smaller doses, a faster onset of the effects, the topical application of a drug to the lungs, and less systematic side effects. In addition, aerosol therapy is painless, and it often results in better clinical outcomes when compared with a much larger oral dose or even with a subcutaneous injection of the drug (Ari et al., 2009). Aerosolized medications include but are not limited to: long- and short-acting adrenergic bronchodilators, long- and short-acting anticholinergic bronchodilators, inhaled corticosteroid, xanthines, mucus-controlling drugs, surfactant agents, mast cell stabilizing agents, antileukotriene agents, and anti-infective agents (Gardenhire, 2007). Short-acting beta agonists such as albuterol are the most common inhaled medication that is being used for NIPPV and aerosol research, and it is administered either by a pMDI or by a small volume nebulizer (SVN) (Branconnier & Hess, 2005; Mukhopadhyay, Dela Pena, Wadden, Procyshyn, & Keang Lim, 2009; Nava, Karakurt, Rampulla, Braschi, & Fanfulla, 2001).
Patients receiving NIPPV may require aerosol therapy for several reasons because NIPPV and aerosol are two modalities that are administered for similar diseases and conditions. COPD and asthma, for example, are two common pulmonary diseases with airflow limitation and may benefit from aerosol therapy, NIPPV, or both. Combining both modalities could result in better deposition and consequently better clinical improvement (Brandao et al., 2009; Nava et al., 2001; Pollack, Fleisch, & Dowsey, 1995) or at least fewer complications from discontinuation of mechanical support. In addition, providing this combination could save therapist time, effort, and cost. Unfortunately, there is a lack of in vivo and in vitro research regarding use of aerosol therapy in patients receiving NIPPV.

**Significance of The Study**

More research is needed to understand the efficacy of aerosol therapy in conjunction with NIPPV. To improve aerosol delivery during NIPPV, the physical and physiological aspects of this type of therapy during NIPPV need to be studied. Additionally, research thus far has not definitively determined which device should be used to optimize aerosol deposition. Clearly, more studies are needed to establish which mask achieves the highest possible aerosol deposition. In addition, no published study has compared the JN, the pMDI, and the VMN. Also, there no study in the literature evaluating the efficiency of the HFA format of pMDI during NIPPV. The efficiency of different masks used during NIPPV is also unknown. No study thus far has looked at the efficiency of the new VMN (NIVO) that is designed specifically for NIPPV.
Purpose of The Study

The purpose of this study was first to determine the efficiency of a JN versus a vibrating mesh nebulizer versus a pressurized metered-dose inhaler, and second to compare the efficiency of the Performax mask, the AF531 oro-nasal mask, and the Performa track mask during NIPPV using two different VMNs.

Research Questions of The Study

The research questions for this study include the following:

1) What is the efficiency of JN, VMN, and pMDI during NIPPV?

2) What is the difference in aerosol deposition among three different masks during NIPPV?
CHAPTER II

REVIEW OF LITERATURE

This literature review examines articles published in the area of aerosol delivery during NIPPV. The search terms used to gather studies for this review included the following: nebulizer, pMDI, SVN, mesh, bronchodilator, nebulization, inhalation therapy, metered-dose inhaler, small volume nebulizer, inhalers, aerosol therapy, noninvasive positive pressure ventilation, mask ventilation, positive pressure respiration, continuous positive airway pressure, positive airway pressure, bilevel positive airway pressure, and noninvasive ventilation. These search terms were utilized together to find articles in different databases such as Cochrane Reviews, Sciencedirect, Web of Science, the Cumulative Index to Nursing and Allied Health Literature, and MEDLINE (pubmed). Relevant articles are presented in the following five sections: (1) bench model studies, (2) clinical studies, (3) studies that include both a bench model and a clinical aspect, (4) NIPPV, and (5) aerosol generators. In vitro studies are included in the bench model section only, and in vivo studies are included only in the clinical section. If the same study includes both in vivo and in vitro components, it is presented in the section entitled “studies including in-vitro and in-vivo components.”


**Bench Studies**

Chatmongkolchart, Schettino, Dillman, Kacmarek, and Hess’s (2002) in vitro study evaluated the effects of ventilator settings and nebulizer position on aerosol bronchodilator delivery during NIPPV. Their model consisted of 1) a double-chamber lung model, 2) a mechanical ventilator, 3) a bilevel positive airway pressure (BiPAP) machine (Respironics, Murrysville, PA), and 4) a small volume nebulizer (SVN) (Micromist, Hudson RCI, Temecula, CA), which was connected either proximally or distally to the BiPAP. Albuterol delivery with BiPAP was evaluated at a respiratory rate of 10 BPM and 20 BPM at inspiratory positive airway pressures and expiratory positive airway pressures (IPAP/EPAP) of 10/5, 15/5, 20/5, 15/10, 20/10, and 25/10 cm H$_2$O, respectively. The albuterol delivery from the SVN with the BiPAP ventilator ranged from 5.2 ± 0.4 to 24.5 ± 1.3% of the nominal albuterol dose. They reported that albuterol delivery was significantly affected by the BiPAP settings, the nebulizer position, and the respiratory rate. They detected the greatest albuterol delivery when the nebulizer was connected at the distal position with a respiratory rate of 20 BPM. Under these conditions, as the inspiratory pressure levels increased, so did the albuterol delivery. In addition, increasing expiratory pressure levels decreased albuterol delivery.

Branconnier and Hess (2005) evaluated the effect of two aerosol delivery devices and the leak port position on albuterol delivery during NIPPV. The authors used a SVN (Micromist, Hudson RCI, Temecula, CA) and a BiPAP machine (BiPAP S/T30, Respironics, Murrysville, PA). They reported that the location of the leak port, the type of aerosol delivery device, and the timing of actuation of the pMDI have an impact on albuterol delivery with NIPPV. They reported three main findings from this study. First,
higher aerosolized bronchodilator delivery was detected when the leak port was in the circuit rather than the mask. Second, the aerosolized bronchodilator delivery using the pMDI with a spacer and the nebulizer was similar when the leak port was in the circuit, but when the leak port was in the mask, delivery was greater with the pMDI. Finally, the researchers detected a significant reduction in aerosolized bronchodilator delivery when the pMDI was actuated during the expiratory phase. Aerosol deposition percentage with both aerosol devices was about 9% when using a spectrum mask (Respironics, Murrysville, PA). When the pMDI was used with a mirage mask (resMed, Poway, CA) it was also 9%; however, it dropped to approximately 4% when an SVN was used with the mirage mask.

Calvert et al. (2006) investigated the differences in inhaled salbutamol during NIPPV at three different aerosol location compared with during spontaneous breathing (without circuit). The authors utilized a Pari COMPAS breath simulator (Pari GmbH, Starnberg, Germany) to model a patient with a sinusoidal breathing pattern. A bilevel ventilator (Knightstar 335, Mallincroft, UK) was connected to the breath simulator via a 187-cm length NIPPV corrugated circuit. The bilevel ventilator was set on spontaneous mode with an IPAP/EPAP of 20/5. Five mg of salbutamol with 2.5 mL normal saline was nebulized for 5 minutes by a JN (Cirrus, Intersurgical Ltd., Wokingham, UK) before the expiration port (position A), after the expiration port (position B) or pre-ventilator (position C). The authors concluded that IM was the highest at position B (647±76 µg) which was slightly more than position B (544±85µg). IM at position C was (267±26µg) which was less than IM (424±61 µg) during spontaneous. Significance can be seen only between position B and C and between B and spontaneous.
Abdelrahim, Plant, and Chrystyn (2010) conducted an in vitro study to detect the differences in IM when delivered during NIPPV at two different positions and via two different nebulizers. The authors contrasted an Aeroneb Professional (Aerogen Inc., Ireland) and a sidestream JN. The positions were either before expiratory port (position A) or after expiratory port (position B). The researchers utilized a breathing simulator machine (Compass; Pari GmbH, Germany) that was connected to a bilevel ventilator (Nippy2; B&D Electromedical, UK) via a 180-cm length of corrugated circuit with a fixed leak port. They found that the deposition was highest with the Aeroneb at position A (2572.2 ±150.9 µg) and second highest with the sidestream at position A (1204.2 ±1613µg).

**Clinical Studies**

Pollack et al. (1995) conducted a randomized prospective clinical study on 100 afebrile, wheezing patients between the ages of 18 and 40 to find out whether beta-adrenergic agonist aerosol is more effective in improving acute bronchospasm if delivered by nasal BiPAP (BiPAP S/T ventilator, Respironics) with an in-line SVN than by an SVN alone. The patients were randomly assigned to receive two doses of aerosolized albuterol via either an SVN alone or an SVN during BiPAP (either nose mask or face mask). In the SVN BiPAP group, aerosol was delivered through the circuit of the BiPAP with an IPAP of 10 cm H₂O and an EPAP of 5 cm H₂O. Arterial blood oxygen saturation (SpO₂), peak expiratory flow rate, heart rate, and respiratory rate were measured before and after each treatment. The researchers found no differences in any of the measures between the two groups except for the percentage of the predicted peak
expiratory flow rate, which was significantly higher in the SVN BiPAP group after each treatment ($p=.0011$) and from their baseline to their final treatment ($p=.0013$).

Nava et al. (2001) conducted a randomized control study on 18 stable patients with COPD to evaluate the feasibility and efficacy of delivery of inhaled salbutamol solution via an SVN with intermittent positive pressure breathing (IPPB) (PR II Respiratory Unit, Puritan Bennett), a pMDI with a spacer (Volumatic, Allen & Hanburys, Greenford, UK) in a spontaneous breathing situation, or a pMDI during NIPPV (Helia, Saime, Savigny Le Temple, France). Patients were randomly assigned to receive one of four possible modalities of treatment for four consecutive days: 1) placebo via a pMDI with a spacer; 2) 400 µg of salbutamol via a pMDI with a spacer during spontaneous breathing; 3) 400 µg of salbutamol via a spacer fitted into the inspiratory limb of the circuit, directly after the wye of the circuit, with use of a pMDI and NIPPV; 4) 5 mg of salbutamol with 5 ml of saline solution delivered by IPPB. The NIPPV settings were as follows: pressure support of $14.3\pm1.8$ cm H$_2$O, a tidal volume guarantee of 10 ml/kg, and inspiratory trigger of 0.5 cm H$_2$O, which were delivered by a full face mask. The authors found that salbutamol delivery during NIPPV is feasible and effective, and showed significant bronchodilation, which was confirmed by the measurement of forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) compared with the placebo group; however, the delivery using pMDIs with a spacer resulted in the best bronchodilation effect.

França et al. (2006) conducted a clinical study on 13 healthy subjects to evaluate pulmonary radioaerosol deposition by a JN during NIPPV (BiPAP synchrony Respironics, Inc.; Murrysville, PA) with an IPAP setting of 12 cm H$_2$O and an EPAP
setting of 5 cm H$_2$O compared with spontaneous breathing nebulization. The radioaerosol used with both groups was Tc99m-DTPA (25 mCi), which was nebulized by a JN (ST3; NS; Sao Paulo, Brazil). Immediately after nebulization, images were taken of the patients’ pulmonary fields using a scintigraphy camera. França et al. compared the pulmonary fields of each group. They reported that there was less radioaerosol deposition during NIPPV compared with spontaneous breathing nebulization ($p<0.001$), and they found a significant correlation between tidal volume and radioaerosol deposition.

Reychler et al. (2007) conducted a clinical study on six healthy subjects to compare lung deposition of amikacin—measured indirectly by urinary excretion—nebulized by a JN (sidestream; Medic-aid; West Sussex) with or without continuous positive airway pressure (CPAP) (Boussignac; Vygon; Belgium) at a pressure of 6 cm H$_2$O. Patients underwent two nebulization sessions (one during CPAP and one spontaneous) in a random order with a one-week washout period between the sessions. After one day of nebulization, urine was collected at each spontaneous urination. The authors found that urine excretion of amikacin in the CPAP group was significantly lower (1.97% initial dose versus 4.88 initial dose, $p<0.001$) compared with those who received nebulization without CPAP.

Brandao et al. (2009) conducted a randomized controlled study on 36 patients with severe asthma to compare the effect of jet nebulization (ST3; NS; Sao Paulo, Brazil) during spontaneous breathing with nebulization during NIPPV (BiPAP synchrony Respironics, Inc.; Murrysville, PA). The pressure settings for NIPPV were an IPAP of 15 cm H$_2$O and an EPAP of 5 cm H$_2$O, or an IPAP of 15 cm H$_2$O and an EPAP of 10 cm H$_2$O. Respiratory rate, heart rate, $S_pO_2$, peak expiratory flow, FEV$_1$, FVC, and forced
expiratory flow between 25 and 75% (FEF\textsubscript{25%-75%}) were measured before and 30 minutes after each treatment. The authors stated that nebulization during NIPPV resulted in significant improvement in peak expiratory flow, FVC, FEV\textsubscript{1}, and FEF\textsubscript{25%-75%} compared with jet nebulization alone. This improvement was better when the delta pressure was smaller and the EPAP was higher. The researchers suggested that this result could be explained by the higher possibility of laminar flow when delta pressure is smaller.

**Studies including in-vitro and in-vivo components**

Parkes and Bersten (1997) conducted in vitro study followed by a clinical study on nine stable asthmatic subjects to investigate the effects of CPAP on aerosol kinetics and bronchodilator efficacy. In their bench model, spontaneous breathing was simulated by using two compartments connected by a bar. The compartments simulated the respiratory muscle and the lung, which was attached to a circuit and a face mask, connected to a ventilator. The ventilator settings were either a fixed tidal volume of 500 ml with a varied inspiratory flow, frequency, and minute volume or a fixed minute volume of 10 liter per minute (LPM) with a varied tidal volume. CPAP was set at a pressure of 10 cm H\textsubscript{2}O with a flow of 50 LPM. Technetium with 3 ml of saline was nebulized with a flow rate of 6 LPM and connected proximally to the mask and the CPAP machine. In this clinical study all subjects underwent nebulization during CPAP and nebulization only. Salbutamol was given at incremental doses of 250 µg, 250 µg, 500 µg, and 1000 µg at 30-minute intervals. For the nebulizer (Bird Micronebuliser, Bird, CA) group, the same doses were given but without the CPAP. FEV\textsubscript{1} was measured after 5 and 30 minutes of nebulization. The researchers found that CPAP resulted in a lower IM\%, from 6.85±1.52 % in the control group to 1.3±0.37% in the CPAP group. In the clinical
study, CPAP did not result in a significant change in the bronchodilation response measured by FEV1 when compared to the control group.

Smedsaas-Löfvenberg, Nilsson, Moa, and Axelsson (1999) conducted an in vitro study followed by a clinical study on five infants to develop and evaluate a safe method to provide nebulization during CPAP. The bench model was conducted by modifying a nasal CPAP system (Infant Flow™; EME, Brighton, UK) to add the ability to deliver nebulization (Aiolos AB, Karlstad, Sweden). The particle size was measured using a Malvern Laser 2600 at a pressure of 2.0-3.0 bars (corresponding to a gas flow of 8.0–10.15 LPM-1). The mass median aerosol diameter (MMAD) of the surfactant was 0.7–0.9 µm, which is very similar to the MMAD for ribavirin generated by the Small Particle Aerosol Generator Model-2. The same model was used to deliver ribavirin to treat five infants with a respiratory syncytial virus infection. All patients made a complete recovery with minimal complications.

Fauroux et al. (2000) conducted in vitro and in vivo studies to evaluate the efficacy of NIPPV (Onyx; Mallinckrodt, Les Ulis, France) in optimizing IM. In the in vitro study, the researchers compared the performance of two actuated nebulizers, of which one was patient-triggered (Optined; Air Liquid Santé, Paris, France) and the other was positive pressure–triggered (Optiplus; Air Liquid Santé). They reported that the MMAD for both nebulizers was very similar (3.21±0.13 and 3.16 ± 0.02, respectively). In the in vivo study, 18 clinically stable cystic fibrosis patients underwent one control session (nebulization alone) and one session of nebulization during NIPPV. Aerosol deposition, which was estimated by radioactive imaging, was significantly higher in the nebulization-during-NIPPV sessions (15.3 ± 8.3 compared with 11.5 ± 5.7, respectively).
The researchers concluded that adding NIPPV to nebulization could enhance total IM without impacting the regional deposition.

**Noninvasive Positive Pressure Ventilation**

Criner, Travaline, Brennan, and Kreimer (1994) conducted a clinical study on nine patients with chronic respiratory failure to evaluate the efficacy of using a full face mask during NIPPV. The researchers utilized three different types of masks: 1) a full face mask (Total, Respironics, Monroeville, PA), 2) a nasal CPAP mask (Respironics), and 3) a nasal/oral mask (Vitalog, Vital Signs). Patients were assigned to receive NIPPV for 20 to 30 minutes via different masks in a random order. In addition, multiple tests were performed on patients before initiating NIPPV and after each session of NIPPV. All masks resulted in a significant improvement in gas exchange, with the best results attained using the full face mask. However, dyspnea, discomfort, and leakage were significant ($p<0.05$) when the full face mask was used.

Plant, Own, and Elliott (2001) conducted a prospective, multicenter, randomized, controlled study on 236 patients with acute exacerbation of COPD. The researchers had two aims. First, they hoped to determine the variables that could be used to divide patients according to their risk of needing invasive mechanical ventilation. The second aim was to ascertain long-term mortality rates associated with using or not using NIPPV. Patients were randomized to receive either NIPPV or a standard treatment. Arterial blood gases and respiratory rate were recorded at admission, after one hour, and after four hours. In the standard treatment group, 27% of the patients required intubation compared to only 15.3% of the NIPPV group ($p<0.02$). The in-hospital mortality rate was 20% for the standard group and 10% for the NIPPV group. The authors recommended the use of
NIPPV as a first line of intervention in addition to standard medical care to manage acute exacerbation of COPD.

Miyoshi, Fujino, Uchiyama, Mashimo, and Nishimura (2005) studied the effects of the gas leak that commonly occurs during NIPPV on triggering function, humidification, and fraction of inspired oxygen (FiO₂) in bilevel pressure ventilators and ICU ventilators. The authors evaluated two ICU ventilators (Puritan Bennett 7200ae and Puritan Bennett 840; Tyco Healthcare; Mansfield, MA) and two bilevel pressure ventilators (BiPAP S/T-D and BiPAP vision; Respironics; Murrysville, PA). The researchers set the machines to an IPAP of 15, an EPAP of 5 cm H₂O, and an FIO₂ of 0.21. A leak was created in the airway opening of the lung model with several holes sizes to allow gas to leak from 1.1 to 44.2 LPM. They reported that bilevel pressure ventilators were able to compensate for all leak sizes adequately, whereas ICU ventilators were not able to do so with large leaks, which resulted in uncontrolled triggering. The authors were able to predict the FiO₂ when the leak was small but were unable to predict it when the leak was large (>15 LPM). Gas leaks caused minimal changes in humidification.

Moerer et al. (2006) conducted an in vitro study to evaluate two types of interface for NIPPV, comparing them with invasive ventilation. The following interfaces were used by the authors: 1) a helmet (Starmed Castar R; Mirandola; Modena, Italy) and 2) a face mask (King Systems Corporation; Noblesville, IN). For the invasive ventilation, the model was connected to an endotracheal tube (Portex, 7.5 mm; Portex, Ltd.; Kent, UK). All systems were evaluated in terms of delay times, pressure time products, and wasted effort during inspiration, defined as the failure of the ventilator-driven chamber to activate the passively driven lung chamber. They reported that delay time was
significantly longer ($p<0.001$) when the helmet was used (144 to 174 ms) compared to invasive ventilation (66 to 76 ms) or the use of the face mask (70 to 74 ms); however, there were no significant differences in mean pressure time products among all the systems. The frequency of wasted efforts (failure of the ventilator-driven chamber to activate the passively driven lung chamber) increased with higher pressure support, higher respiratory rate, lower sensitivity, higher compliance, and the helmet interface.

Conti et al.’s (2007) clinical study compared the efficacy of NIPPV delivered by helmet (CaStar, Starmed, Mirandola, Italy) versus face mask (Vital Signs, Totowa, NJ, or Dar-Tyco, Mirandola, Italy) in 50 patients with acute respiratory failure after abdominal surgery. The control group of 25 patients was selected from a historical group based on numerous factors to match with the intervention group. The matching was based on age, simplified acute physiology score II, and the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$). The ventilator (300, Siemens, Uppsala, Sweden) was started at IPAP of 10 cm H$_2$O with an incremental increase to achieve patient comfort of less than 25 BPM. EPAP was increased up to 12 cm H$_2$O in order to maintain $\text{SpO}_2$ over 90% with the minimal $\text{FiO}_2$ possible. The authors reported that mask intolerance, major leaks, or ventilator-associated pneumonia were significantly higher in the face mask group ($p<0.03$).

Roy, Cordova, Travaline, D’Alonzo, and Criner (2007) conducted a clinical study on 10 nonambulatory patients with acute respiratory failure to determine the effectiveness of a total face mask in the application of NIPPV. None of the patients were able to tolerate NIPPV via nasal mask (Respironics, Inc., Monroeville, PA) or oro-nasal mask (Respironics, Inc., Monroeville, PA); however, eight out of the 10 patients were managed
successfully when NIPPV was delivered via a total face mask (Respironics, Inc., Monroeville, PA), and the other two required endotracheal intubation due to excessive secretions. Patients were ventilated by NIPPV (BiPAP, Respironics, Inc., Monroeville, PA) with an initial IPAP of 21 cm H$_2$O and EPAP of 3 cm H$_2$O with an average delta pressure of 18±4 cm H$_2$O. The authors suggested using a total face mask with patients who could not tolerate NIPPV with a nasal or oro-nasal mask.

**Aerosol Generators**

Deerojanawong et al. (2005) conducted a double-blind, randomized controlled trial on 47 young children with wheezing to compare the efficacy of salbutamol aerosol therapy delivered by either a pMDI or a JN. Each patient was given either a placebo pMDI followed by a jet nebulization treatment or a placebo jet nebulization followed by a pMDI. Clinical outcomes were quantified by measuring each patient’s heart rate, respiratory rate, clinical scores, SpO$_2$, and pulmonary function before and 30 minutes after each treatment. The authors concluded that there was no statistical difference between the groups in terms of clinical outcomes; however, heart rate was significantly higher in the jet nebulization group when compared with the pMDI group.

Pitance et al. (2010) conducted both in vitro and in vivo studies to compare the IM and urinary drug concentration of amikacin in three aerosol delivery systems: a standard JN (sidestream, Philips-Respironics, Pittsburgh, PA) with and without a 110-ml corrugated piece of tubing and a VMN (e-Flow Rapid, PARI, Pharma GmbH, Munich, Germany). All systems were assessed for particle size distribution using a Malvern Mastersizer-X laser particle sizer (Malvern Instruments Ltd., Worcestershire, UK) during the in vitro study; however, during the in vivo study the IM was measured indirectly by
the urinary excretion of amikacin. The authors reported that during the in vitro portion of the study, the IM% of the nominal dose was approximately 40% for the mesh nebulizer, 25% for the JN with the corrugated tube, and 15% for the JN alone; however, there was no significant difference in MMAD among all three systems. The daily percentage of amikacin from the initial dose was 11.6% with the mesh nebulizer, 8.2% with the JN with the corrugated tube, and 6.15% with the JN alone. Both results suggest that the mesh nebulizer was able to deliver the highest amount of aerosol mass among the three systems.

Skaria and Smaldone (2010) conducted an in vitro study comparing IM, residual activity, MMAD, and run time (which is the time required to provide the nebulization by the system) with a radiolabeled albuterol for four aerosol systems. The systems compared in this study included a sidestream JN (Philips/Respironics, Parsippany, NJ), a breath-enhanced nebulizer (Pari LC Plus, Pari Respiratory Equipment, Midlothian, VA), and a mesh nebulizer (Omron Healthcare, Inc., Bannockburn, IL), which was tested in both the tilted and the horizontal positions. All systems were ventilated with a Harvard pump and set to simulate a COPD patient with a tidal volume of 450 ml, a respiratory rate of 15 BPM, and a duty cycle of 0.35. Particle distribution was quantified by using low flow cascade impaction. The authors found that the IM by the Omron and Pari were comparable (20% of the nominal dose) and higher than the sidestream (10%). However, MMADs were comparable for all systems (1.3–2.4) µm, but variability (1.9–3.5) µm was higher for the Omron in the horizontal position. Residual activates for the Omron in the tilted position were 25% CI (22–32) and 22% CI (18–25) in the horizontal position. Residual activates for the Pari LC were 57% CI (55–60) and 47% CI (45–49) for the
sidestream. The run time was significantly lower for the Omron in both positions compared with the JNs; however, it was about three times greater in the tilted position.

In an in vitro study, Ari, Areabi, and Fink (2010) compared the performance of four aerosol generators at three different locations in humidified and nonhumidified circuits during adult mechanical ventilation. They examined four aerosol generators—a JN, a VMN, an ultrasonic nebulizer, and a pMDI with a spacer—at three different locations: 1) between the endotracheal tube and the Y-piece, 2) 15 cm from the Y-piece, and 3) 15 cm from the ventilator. The ventilator settings were a tidal volume of 500 ml, a ramp flow pattern, 15 BPM, a peak inspiratory flow of 60 LPM, and a positive end expiratory pressure of 5 cm H2O. The drug deposition was collected by an absolute filter distal to an 8.0-mm endotracheal tube and was measured by spectrophotometry (276 mm). The VMN was able to deliver 30.2% ±1.0, which was the highest IM% throughout the study, at location 2 with a nonhumidified circuit; in contrast, the pMDI delivered the least IM% 2.5% ± 0.8 at location 3 with a heated circuit. The authors reported that the humidified circuit had the overall effect of decreasing IM in all positions and with all generators.

Ari, Atalay, et al. (2010) conducted an in vitro study to determine the impact of nebulizer type, position on the ventilator circuit, and bias flow on aerosol delivery in simulated and mechanically ventilated pediatric and adult lung models. The study used a JN and a VMN. The JN was set at 15 cm proximal to the wye (position 1) or 15 cm prior to the heated humidifier (position 2). The VMN was attached directly to the wye, at the inlet of the humidifier. Bias flow was either 2 liters per minute (LPM) or 5 LPM. The highest IM% 23.8% ±1.0, was attained with the adult lung model at position 2 with a 2
LPM bias flow, delivered by VMN; in contrast, the lowest IM%, 3.8 %± 0.3, was measured using the pediatric lung model at position 1 with a 5 LPM bias flow delivered by JN. In all conditions, the IM was two- to four folds greater when using the VMN.
CHAPTER III

METHODOLOGY

Lung Model

This model consists of a BiPAP ventilator (BiPAP S/T30, Respironics, Murrysville, PA) and a single-limb NIPPV circuit (Philips, Respironics, PA). In this in-vitro model, a breathing adult was simulated. The BiPAP machine was set on the spontaneous/time mode with a respiratory rate of 15 BPM and an inspiratory time of 1.0 second, with pressures settings of IPAP/EPAP 20/5 cm H₂O. The single-limb NIPPV circuit was connected between the BiPAP machine and the mask, which was tightly strapped to the head of the manikin. Each aerosol generator that was used in this study was attached between the mask and the single-limb circuit.

First Experiment

Aerosol Generators Type, Dose, Location, and Operation

Three different aerosol generators were investigated in this study: 1) a JN (Micro Mist, Hudson RCI, Temecula, CA), 2) a pMDI (ProAir HFA, Teva Specialty Pharmaceuticals, Atlanta, GA) with a spacer, and 3) a VMN (Aeroneb Solo, Aerogen, Mountain View, CA). All generators were placed between the AF531 oro-nasal mask (Respironics, Inc., Murrysville, PA) and the circuit. The JN was pressurized with 8 LPM O₂ and a 2.5 mg/3 ml unit dose of albuterol (Nephron Pharmaceuticals, Orlando, FL) and connected at the vertical position (Figure 1). Nebulization continued until sputter. The pMDI was shaken and primed, then connected at the same location (Figure 2). The pMDI actuation synchronized at the beginning of the inspiratory cycle for a total of four actuations, separated by at least 15 seconds. The pMDI was connected to a spacer either
at the normal position (recommended by the company) which was abbreviated as pMDI-N or the reversed position (pMDI-R). The VMN was connected at the same location, and a 2.5 mg/3 ml unit dose was placed into the nebulizer (Figure 3). The nebulizer was run continuously until sputter.

*Figure 1.* Lung model with the jet nebulizer.
Figure 2. Lung model with the pMDI.

Figure 3. Lung model with the vibrating mesh nebulizer.
Second Experiment

Masks Types

The same lung model was reassembled for the second experiment. Two different VMNs were used: an Aeroneb Solo (Aerogen, Mountain View, CA) and a NIVO (Phillips Respironics, Ireland). Three masks were used: 1) a Performax mask (Respironics, Inc., Murrysville, PA), 2) an AF531 oro-nasal mask (Respironics, Inc., Murrysville, PA), and 3) a Performa track mask (Respironics, Inc., Murrysville, PA). The Performax mask was investigated with both mesh nebulizers (Aeroneb Solo and NIVO). The Performa track mask was only tested with the Aeroneb Solo due to the inability to connect with the NIVO.

Figure 4. From left to right, Performax mask, AF531 oro-nasal mask, Performa track mask

Measurement of Aerosol deposition

An absolute filter (Respirgard II, 303, Vital Signs, Totowa, NY) was attached and placed at the wye connection, where two simulated bronchi from the manikin meet. After each test was completed, the filter was shaken for at least one minute after being washed with 0.1 molar N HCl. The concentration of albuterol from the filter was measured via a spectrophotometer (Beckman Instruments, Fullerton, CA).
Data Analysis

Albuterol deposition was quantified and reported as a percentage of the nominal dose. Data analysis and graphs were created using Statistical Package for the Social Sciences (IBM SPSS, 18.0, Armonk, NY) and Microsoft office Excel (2007, Redmond, WA). Means and standard deviations were calculated for the three generators. A one-way ANOVA test was used not only to compare the means of albuterol deposition of the three generators on the first experiment, but also to compare means of albuterol depositions and residual volume among the three different masks on the second experiment. An independent t-test was used to compare residual volume in the VMN and the JN on the first experiment and to compare the Aeroneb Solo and the NIVO in the second experiment. A significance level of 0.05 was used for all comparisons.
CHAPTER IV

RESULTS

In the first experiment, descriptive statistics were computed for IM, IM%, and residual volume (Table 1). In addition, inferential statistics were used to compare the means and to identify the significance levels IM, IM%, and residual volume. The ANOVA comparing the means of IM during NIPPV varied significantly ($p<0.05$): the JN and the VMN resulted in a significance level of $p=0.005$; the JN and the pMDI in the reversed position (pMDI-R) had a significance level of $p=0.002$; the JN and the pMDI in the normal position (pMDI-N) was significant at the $p=0.001$ level; the VMN and the pMDI-R resulted in a significance level of $p=0.002$; and the VMN and the pMDI (in both positions) had a significance level of $p=0.002$. The difference between the pMDI-N and the pMDI-R was not significant ($p=0.253$). Of the delivery devices tested, the VMN produced the highest IM (0.72 mg ± 0.48 mg) with the highest IM% (28.83% ± 1.93%). In addition, the VMN had a significantly lower residual volume than the JN ($p=0.000$). The mean residual volume of the VMN was 0.10 ml ± 0.069, whereas the mean residual volume of the JN was ml 1.65 ± 1.14.
Table 1

Means and SDs of inhaled mass, inhaled mass percent and residual volume of each aerosol device used in this study. JN: jet nebulizer VMN: vibrating mesh nebulizer,
pMDI-N= pMDI normal position, pMDI-R: pMDI retrograde position

<table>
<thead>
<tr>
<th></th>
<th>JN</th>
<th>VMN</th>
<th>pMDI-N</th>
<th>pMDI-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled Mass (mg)</td>
<td>0.33 ± 0.02</td>
<td>0.72 ± 0.05</td>
<td>0.10 ± 0.01</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>Inhaled Mass Percent (%)</td>
<td>13.12 ± 0.72</td>
<td>28.83 ± 1.93</td>
<td>23.53 ± 2.03</td>
<td>21.38 ± 0.32</td>
</tr>
<tr>
<td>Residual volume (g)</td>
<td>1.65 ± 0.14</td>
<td>0.10 ± 0.07</td>
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Figure 5. Inhaled mass percentage differences between devices.

* p<0.05
In the second experiment, results indicate that aerosol delivery during NIPPV with the three different masks and the two different VMNs varied significantly \( (p<0.05) \). However, the only statistically significant relations are between the oro-nasal mask–Aeroneb Solo VMN setup and each of the other setups. For example, the oro-nasal mask–Aeroneb Solo setup compared with the Performax mask–Aeroneb Solo was significant at the \( p=0.003 \) level. This same setup had the following results when compared with other combinations: the oro-nasal mask–NIVO VMN \( (p=0.023) \), the Performax mask–NIVO VMN \( (p=0.001) \), and the Performa track mask–Aeroneb Solo VMN \( (p=.000) \). All other relations were not significant.

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 provide a close IM%. Oro-nasal mask with Aeroneb solo
provided the highest aerosol deposition and may be consider as a first option for aerosol therapy during NIPPV. Other masks did not differ statistically. Therefore, the mask selection should be based on patient’s need and comfort level, and mask availability.

Table 2

* Inhaled Mass and Inhaled Mass Percent Among the Five VMN–Mask Combinations

<table>
<thead>
<tr>
<th></th>
<th>Performax mask–NIVO VMN</th>
<th>Performax mask–Aeroneb Solo VMN</th>
<th>Oro-nasal mask–NIVO VMN</th>
<th>Oro-nasal mask–Aeroneb Solo VMN</th>
<th>Performa track mask–Solo VMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled mass</td>
<td>0.49 ± 0.026</td>
<td>0.53±0.048</td>
<td>0.58±0.018</td>
<td>0.72±0.048</td>
<td>0.46±0.062</td>
</tr>
<tr>
<td>Inhaled mass %</td>
<td>20 ± 1.05</td>
<td>21±1.93</td>
<td>23±.70</td>
<td>29±1.92</td>
<td>19±2.46</td>
</tr>
</tbody>
</table>

*Figure 7. Inhaled mass percentage differences among different masks. * p<0.05*
CHAPTER V
DISCUSSION

The findings of this study demonstrate the efficiency of aerosol devices and masks used during NIPPV. The VMN provided the highest IM and IM\% to the filter (0.72 mg ± 0.05 mg, 28.83 % ± 1.93\%, respectively). In comparison, the JN provided the second-highest IM with the lowest IM\% (0.33 mg ± 0.02 mg, 13.12% ± 0.72\%, respectively). The pMDI, in both orientations, delivered the lowest IM with the second-highest IM\%. The VMN was more efficient than the JN by providing significantly lower residual volumes (0.10 ± 0.07 mL). In the second experiment, the oro-nasal mask with the Aeroneb Solo VMN provided the highest IM with the highest IM\% (0.72 ± 0.05, 28.83% ± 1.93\%, respectively). This mask resulted in a significant difference when compared with any other mask or setup used in this study.

This study used NIPPV machine that is commonly used in acute and chronic conditions with ventilator settings that have been used in four published in vitro aerosol studies focused on using NIPPV (Abdelrahim et al., 2010; Branconnier & Hess, 2005; Calvert et al., 2006; Chatmongkolchart et al., 2002). When different aerosol devices and masks were utilized during NIPPV in an adult lung model, the IM varied between 0.09 mg and 0.72 mg, representing 13\% to 29\% of the emitted or nominal dose. The second experiment found the highest IM when the oro-nasal mask was used with the Aeroneb Solo VMN (0.72 mg ± 0.05 mg), which was approximately two-fold higher than with the JN and seven-fold higher than with the pMDI at either position. These findings are consistent with those of Ari, Areabi, and Fink (2010) when comparing VMN, pMDI and
JN. Two other studies, however, reported considerably higher IM. Using a VMN, Abdelrahim et al. (2010) reported an IM of 2572.5 µg ±150.9 µg using a JN, Calvert et al. (2006) found an IM of 647 µg ±67 µg. The adult lung model is the key to understanding the difference in results between these studies and the present study. Abdelrahim et al. and Calvert et al. both used a model in which they attached the inhalation filter directly to the circuit; in this study, the inhalation filter was attached to the wye connection, distal to the two simulated main bronchi. In addition, both of the other studies used a higher nominal dose than in the present model, which clearly could have increased aerosol deposition. Additionally, Abdelrahim et al. used a different medication (terbutaline 5.0 mg), which could have different chemical and physical proprieties than albuterol. Theoretically, our study model provides a more realistic estimation of the human lung configuration with inhaled medications.

Branconnier and Hess (2005) utilized a more realistic model with an actual non-invasive mask when compared with other studies. Their findings demonstrate a better aerosol deposition with the spectrum mask (which had a leak port at the circuit) when compared with the mirage mask (leak port at the mask); however, their IM with Spectrum mask (450 µg for the JN and 50 µg for the pMDI) was not similar to ours. This difference might be explained by their use of an invasive ventilator (model 840 Puritan-Bennett, Carlsbad, CA). Non-invasive ventilators support leak control, but invasive ventilators—like the one used by Branconnier and Hess—may not. This could lead to less bias flow in the circuit, which has been shown to have an impact on aerosol delivery (Ari, Atalay, et al., 2010). In addition, the Branconnier and Hess’s study was published before the introduction of pMDI with hydrofluoroalkane (HFA), which is well-known to promote
better aerosol delivery when compared with chlorofluorocarbon. Indeed, they used higher nominal dose (5.0 mg compared to 2.5 mg) and lower IPAP (15 cm H₂O compared to 20 cm H₂O). Interestingly, Chatmongkolchart et al. (2002) reported about 25% IM% compared to approximately 13% in our study with the same JN (Micromist); however, they used a larger albuterol dose (5.0 mg compared to 2.5 mg) with a higher respiratory rate (20 BPM compared to 15 BPM). Both factors can lead to higher aerosol deposition. In addition, they did not utilize a noninvasive mask in their model, and the filter was connected directly to the circuit.

Our study used S/T mode with IPAP/EPAP of 20/5 cm H₂O and RR 20 BPM with no spontaneous effort. Those fixed settings may not mimic the clinical dynamic situation for patient with airway limitation.

For further studies, we suggest studying the effect of humidification on IM during NIPPV. Another suggestion is to study the effect of pMDI doses on aerosol delivery during NIPPV.

In conclusion, the JN was less efficient than the VMN and the pMDI in either orientation. The type of aerosol device used during NIPPV influenced aerosol delivery in this simulated adult lung model. Oro nasal mask with Aeroneb Solo VMN provided the highest aerosol delivery. 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 a clinical judgment.
REFERENCES


