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How to optimize aerosol drug delivery during noninvasive ventilation: What to use, how to use it, and why?

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Abstract:

Much evidence supports the use of non-invasive ventilation (NIV) in patients who have acute and chronic respiratory failure and aerosolized medications are increasingly used in this patient population. Successful application of aerosol therapy during NIV depends on the effectiveness of the drug deposition in the lungs. Previous evidence showed that many factors impact aerosol delivery to patients receiving NIV. Those factors include mode of ventilation, ventilator parameters, type of ventilator circuit, the position of the aerosol device, the location of leak port, type of exhalation valve, humidity, enhanced condensational growth, type of aerosol device, and interface as well as delivery technique. The purpose of this paper is to review the available evidence related to aerosol therapy during NIV and provide recommendations to optimize aerosol drug delivery to patients receiving NIV.

Keywords:

Aerosols, metered-dose inhalers, nebulizers, noninvasive ventilation and drugs

Introduction

Noninvasive ventilation (NIV) has gained popularity in the treatment of patients with acute and chronic respiratory failure because it prevents complications of endotracheal intubation as well as improves gas exchange, work of breathing, and mortality.[1-7] Aerosolized medications remain the main treatment modality for this patient population because most patients receiving NIV for respiratory failure also need aerosol therapy. Previous research has shown that aerosol drug delivery during NIV is feasible and effective in patients with asthma and chronic obstructive pulmonary disease (COPD).[8-10]

Although evidence on aerosol drug delivery during mechanical ventilation is well described, clinical studies on patients receiving aerosol therapy during NIV are still limited. Previous *in vitro* studies in this area of research showed that many factors impact aerosol drug delivery to this patient population. Those factors include mode of ventilation, ventilator parameters, type of ventilator circuit, the position of the aerosol device, the location of leak port, type of exhalation valve, humidity, enhanced condensational growth, type of aerosol device, and interface as well as delivery technique.[6,11-15] Despite a strong rationale and frequent use of aerosolized medications in patients receiving NIV, clinicians need a greater understanding on what to use, how to use it, and why in patients receiving aerosol therapy during NIV. Therefore, the purpose of this paper is to review the current knowledge of aerosol drug delivery during NIV and provide strategies to optimize aerosol drug delivery in this patient population.

Mode of Ventilation

Although the selection of a ventilator mode during NIV is important, research on the

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effect of different NIV modes on aerosol drug delivery is still limited. Bi-level positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) are commonly used during NIV. In BiPAP, two different levels of positive airway pressure are applied to the airway during inspiration and expiration. As opposed to BiPAP, CPAP has the same amount of positive pressure applied to the airways during inspiration and expiration.

Using a bench model of spontaneous breathing, Parkes and Bersten determined the efficacy of bronchodilator therapy during CPAP delivered by face mask.[8] They then conducted a clinical study to determine the responses to incremental doses of inhaled bronchodilators in nine patients with stable asthma using the jet nebulizer alone (control) and the jet nebulizer coupled with CPAP and a tight-fitting face mask. While aerosol delivery with CPAP decreased from 6.85% to 1.3% in the bench study, the findings of their clinical study showed a significant response to aerosol therapy for CPAP and the control conditions. They also reported that the increase in the magnitude of forced expiratory volume in 1 s (FEV_1) and the shape of the dose-response curve were identical in both groups.

Reychler *et al*. compared lung dose with jet nebulizer alone or combined with CPAP device (Boussignac) in 6 healthy volunteers by measuring drug concentration excreted in urine to determine lung deposition indirectly.[16] They found that aerosol deposition in healthy lungs is 2.5-fold less with CPAP than nebulizer alone. However, the placement of the Boussignac device might have influenced the function and performance of the breath-actuated nebulizer which may have confounded the results of this study.

In a randomized clinical study on patients with asthma admitted to the emergency department, Pollack *et al*. compared aerosol drug delivery with BiPAP and nebulizer alone.[9] They reported a significant improvement in peak expiratory flow (PEF) from 211 to 357 L/min during BiPAP and from 183 to 280 L/min during spontaneous breathing with nebulizer alone. Changes in oxygen saturation, heart rate, and breathing frequency were similar in both groups of this study.[9] Previous evidence also reported a greater improvement in FEV_1, forced vital capacity (FVC), PEF, and inspiratory capacity of patients with asthma after bronchodilator administration combined with NIV.[17-20]

Maccari *et al*. compared radioaerosol deposition during spontaneous breathing, CPAP at 10 cm H_2O, and BiPAP with inspiratory positive airway pressure/positive expiratory positive airway pressure (IPAP/EPAP) of 15/5 cm H_2O in 13 healthy controls.[21] The findings of their study showed no difference between radioaerosol deposition in the trachea and both the right and left lungs. They also reported that aerosol drug delivery did not decrease during BiPAP or CPAP.[21]

Ventilator Parameters

Delivery efficiency of aerosol devices improved with higher IPAP and lower positive expiratory pressure (EPAP) during NIV.[22] Because an increase in EPAP leads to an increased retrograde flow during expiration with aerosol leakage through the leak port, using higher EPAP levels reduces aerosol delivery during NIV.[22] In an *in vitro* study, Sutherasan *et al*. found that aerosol delivery efficiency was greater with IPAP/EPAP of 15/5 cm H_2O than 10/5 cm H_2O, 15/10 cm H_2O and 20/10 cm H_2O.[23]

Another ventilator parameter that impacts aerosol drug delivery during NIV is inspiratory flow rate. The higher the inspiratory flow, the higher the turbulent flow that produces greater inertial forces causing aerosol deposition in more central airways.[24-26] França *et al*. studied the relationship between tidal volume and radioaerosol deposition in 13 healthy controls and compared lung deposition during jet nebulizer combined with NIV versus spontaneous breathing.[27] While they found a significant relationship between tidal volume and lung dose during spontaneous breathing, there was no correlation between these parameters during NIV. Even though a high inspiratory flow increased tidal volume, it did not lead to an improvement in pulmonary deposition during NIV.[27]

Type of Ventilator Circuit

Noninvasive ventilators have either a single-limb or a double-limb circuit. For instance, bi-level ventilators are commonly used during NIV and employ a single limb circuit with a leak port that serves as an exhalation port for the patient. Critical care ventilators can also be used for NIV. Unlike bi-level ventilators, they have dual limb circuits with inspiratory and expiratory valves using separate hoses for gases that are used in inspiration and expiration. While the majority of previous research on NIV utilized single-limb circuits, there is no study in the literature that compares two types of ventilator circuits on aerosol delivery during NIV.

Position of Aerosol Device

Aerosol devices are usually placed in three different locations on the ventilator circuit: (1) attached to the vented mask with leak port, (2) located between the leak port and ventilator on the NIV circuit, or (3) placed between the leak port on the circuit and unvented mask. Previous evidence showed that the optimum position

of aerosol devices during NIV is between the leak port and the mask.[9,28-33] When a nebulizer is attached to a vented mask with leak port, aerosol loss occurs both in inspiration and expiration. Therefore, placing a nebulizer to this position leads to a significant reduction in aerosol drug delivery during NIV.

Ari *et al*. showed that the nebulizer position impacts aerosol delivery during mechanical ventilation. Since some of the aerosol diffuses in the expiratory limb in inspiration, they are blown away during expiration in ventilator-dependent patients. Therefore, placing the nebulizer near the ventilator improves aerosol drug delivery during adult and pediatric mechanical ventilation because the ventilator circuit can serve as a storage.[34,35] However, this is not the case with bi-level ventilators because aerosol leaks into the environment during inspiration and expiration with the placement of a nebulizer between the leak port and the ventilator. Unlike mechanical ventilation, the storage function of the circuit is poor due to gas leakage and flow through the circuit with leak compensation during NIV. Therefore, nebulizer placement distant from the patient leads to greater aerosol loss due to the presence of leak port in the NIV circuit that creates a bias flow toward the exterior and gas leakage on the circuit.

When the nebulizer is placed between the leak port and the unvented mask, inspiratory pressure used during NIV moves aerosols to the patients. While some of the aerosols escape through the leak port on the circuit during expiration, others accumulate in the tubing and are delivered in the next inspiration. Peng *et al*. showed that adding an extension tube of 15 cm in between the leak port and the nebulizer reduces aerosol loss from the leak port because the extension tube acts as a reservoir.[28] CO_2 rebreathing may be a concern when a 15 cm extension tube is added to the circuit. However, previous research showed that use of a face mask can increase CO_2 rebreathing approximately 3 mL with each breath.[36,37] Therefore, Peng *et al*. reported that using a 15 cm extension tube may have a small effect on CO_2 rebreathing.[28]

Figure 1: Single arch exhalation port

Location of the Leak Port

The leak port allows gas washout during expiration and its position impacts the efficiency of aerosol device during NIV. It is incorporated either in the mask or within the ventilator circuit. More aerosol is delivered when the leak port is in the circuit instead of the mask.[38] Therefore, the ventilator circuit with leak port should be utilized for aerosol drug delivery in patients receiving NIV. While delivery efficiency of the nebulizer is greater than pressurized metered-dose inhaler (pMDI) when the leak port is located in the circuit, its efficiency decreased >50% due to greater aerosol waste through the leak port on the mask.[38] Therefore, clinicians may need to increase the dose if the mask with leak port is used with the nebulizer to deliver aerosolized medications to patients receiving NIV.

Type of Exhalation Valve

There are different types of exhalation valves used in leak ports. The plateau exhalation port, single arch exhalation port, and whisper swivel are the most commonly used exhalation valves during NIV. Figure 1 shows the single arch exhalation port. Dai *et al*. compared the effect of these exhalation valves on aerosol drug delivery to simulated spontaneously breathing adults receiving NIV.[39] They reported that aerosol delivery with the single arch exhalation port was greater than plateau exhalation port and whisper swivel at nebulizer position between the leak port and lung model.[39]

Humidity

Inhaled air is humidified during its passage through the nose. However, high inspiratory rates used during NIV may overwhelm the humidication capacity of the nose and lead to throat irritation as well as an increase in nasal resistance that may impact the benefits of bronchodilator therapy.[40-44] Thus, humidification may be needed in patients receiving NIV in order to avoid the undesirable effects of inhaled dry gas and improve patient comfort.

Regarding the effect of humidification on aerosol delivery, previous research reported a decrease up to 50% in aerosol deposition with the use of heated and humidified ventilator circuits.[34,45-49] However, these studies utilized nonheated/nohumidified circuits and none of these simulated exhaled humidity in their lung models. For the first time, Ari *et al*. simulated exhaled heat and humidity using an *in vitro* lung model to better simulate patient aerosol interactions

and to understand the impact of exhaled, heated and humidified gas on aerosol delivery to critically ill patients with tracheostomy.[50] The findings of their study showed a reduction of up to 44% with exhaled humidity.[50] The other follow-up studies conducted by the same group confirmed that use of lung models with unheated/nonhumidified exhalation in previous *in vitro* studies may overestimate aerosol drug delivery to patients.[51-53] Similarly, no significant difference was found in the urinary excreted albuterol after inhalation between humidified and dry conditions during NIV.[44,54] Therefore, there is no need to turn off the humidifier for aerosol drug delivery to patients receiving NIV.

Enhanced Condensational Growth

Deposition of aerosols in nasal passages significantly decreases lung dose and leads to a reduction in efficacy of brochodilator compared to inhalation with a mouthpiece.[55,56] Longest *et al*. developed a novel concept of aerosol drug delivery that provides a submicrometer aerosol to one nostril at slightly subsaturated conditions and delivered a humidified airstream saturated with water vapor to the other nostril using a nose, mouth, and throat model during NIV.[57-59] Since the nasal septum separated the two streams of aerosols, the submicrometer aerosol retained its small size and reduced nasal deposition from 72% to 14%.[57]

Type of Aerosol Device

Nebulizers and pMDIs are employed to deliver aerosolized medications to patients receiving NIV. Alquaimi *et al*. compared delivery efficiency of pMDI, jet and mesh nebulizers by using a spontaneously breathing adult lung model receiving NIV.[60] The findings of this study showed that aerosol delivery with the jet nebulizer is lower than pMDI and the mesh nebulizer.[60] Aerosol deposition obtained with the mesh nebulizer is greater than the pMDI because of the higher nominal dose used with the nebulizer. Despite a lower dose delivered with pMDI, Nava *et al*. showed a significant bronchodilator effect in stable patients with COPD receiving bronchodilators through pMDI with spacer during NIV.[61] Therefore, pMDIs can be effectively used in patients receiving NIV.

Aerosol drug delivery with vibrating mesh nebulizers was 3-to 5-fold greater than that with jet nebulizers because of a smaller dead volume of mesh nebulizers.[30,33,62-65] Dead volume, known as residual volume, is the amount of drug remaining in the nebulizer cup at the end of therapy. While the dead volume of jet nebulizers range from 1 mL to 2.5 mL, the greater the dead volume the less amount of drug delivered to patients during aerosol therapy. Michotte *et al*. compared inhaled and lost doses of 3 mesh nebulizers (Aerogen Solo, Aerogen Pro and NIVO), one ultrasonic nebulizer (Servo Ultra) and one jet nebulizer (Sidestream) at different positions in an adult lung model.[32] The findings of their study showed that the jet nebulizer had the highest lost dose during expiration, whereas the ultrasonic nebulizer had the highest total wasted dose in the same position. The NIVO and Aerogen Solo were the most efficient nebulizers when they were positioned between the leak port and the lung model.

Saeed *et al*. compared delivery efficiency of different designs of jet and mesh nebulizers during NIV.[63] The findings of their study showed a significant difference on aerosol delivery with different designs of jet nebulizers while aerosol deposition obtained with mesh nebulizers was the same with each design tested in this study.

Type of Interface

Successful administration of NIV depends on the patient's tolerance of an interface. Nasal pillow or plugs, nasal mask, oronasal mask, full face mask, and helmet are the interfaces designed for NIV. While previous research showed equal improvement in arterial blood gases with nasal and oronasal masks, the oronasal mask is commonly used by clinicians.[66-68] Ari *et al*. compared bronchodilator delivery with nasal pillow, nasal mask, oronasal mask, and full face mask using a simulated adult lung model receiving NIV. While aerosol delivery with the nasal pillow was significantly lower than other interfaces tested in this study, the nasal mask and oronasal mask had a similar delivery efficiency.[69] The full face mask and helmet cause aerosolized medications deposit in the eye; therefore, they should not be used for aerosol therapy during NIV. Furthermore, the results of a bench study showed that the helmet leads to the worst patient-ventilator interaction, suggesting that the face mask should be considered for delivering NIV to children at high inspiratory rate.[70]

While there are several adult interfaces that can be used during NIV, only few pediatric interfaces are available on the market. Children are nose breathers and the nasal mask is commonly used with this patient population during NIV. However, each nasal mask has different internal volume and may behave differently in children. According to a pediatric *in vitro* study that compared delivery efficiency of the standard oronasal mask, oronasal mask with nose cushion, and nasal mask; aerosol deposition with the standard oronasal mask was greater than the other interfaces used with jet and mesh nebulizers in a pediatric lung model receiving NIV.[71]

Delivery Technique

In the past, when inhaled medications needed to be delivered to patients receiving NIV, clinicians removed

the mask and provided aerosol therapy in the traditional way. However, the problem with this technique is that patients decompensate with the discontinuation of NIV.[14] Aerosol drug delivery during NIV is a more effective method than conventional aerosol therapy that is administered between NIV sessions. Although combining aerosol therapy and NIV did not improve radioaerosol pulmonary deposition, there was a clinical improvement of pulmonary function of patients receiving aerosol therapy during NIV.[18,27] For instance, tidal volume, minute ventilation, FEV_1, FVC, PEF, and inspiratory capacity of patients in the NIV plus nebulization group significantly increased in patients with asthma compared to patients received nebulization only.[9,18,27] The addition to aerosol therapy to NIV can improve lung function because NIV unloads the fatigued respiratory muscles and helps patients easily reach total lung capacity and improved FEV_1.[9,19] Previous research also showed a reduction in symptoms and bronchial obstruction as well as an improvement in patient's respiratory discomfort and a decrease in intubation rate.[17,19] Table 1 lists the steps of optimum technique for aerosol drug delivery with pMDIs, jet and mesh nebulizers used during NIV.

When a pMDI is used for aerosol drug delivery during NIV, the canister must be removed from the actuator and attached to an adapter or spacer designed for mechanically ventilated patients. Although there is no studies comparing different types of spacers used during NIV, several studies on mechanical ventilation showed 4-to 6-fold more areosol deposition with chamber-shaped spacers.[45,72-75] Therefore, it is logical to prefer a chamber shaped spacer to improve aerosol drug delivery to patients receiving NIV. Timing with pMDI actuation is important because aerosol delivery with pMDI was significantly decreased when the pMDI was actuated during expiration instead of the beginning of inspiration.[38] Therefore, it is essential to synchronize pMDI actuation with the precise onset of inspiration when a pMDI is used for aerosol therapy during NIV. Otherwise, short delays of 1–1.5 s between pMDI actuation and inspiration will significantly decrease delivery efficiency of pMDIs.[45] When a high dose is needed for the treatment of a patient receiving NIV, clinicians can either use a nebulizer or increase the number of pMDI actuations.

As discussed earlier, jet nebulizers are the least efficient aerosol device secondary to their large dead volumes. Previous research reported that increasing fill volume improves delivery efficiency of jet nebulizers significantly.[44,76,77] While this strategy can be used to improve aerosol delivery with jet nebulizers during NIV, there is no need to increase the fill volume of mesh nebulizers because they are not affected by change of fill volume and have similar efficiency with different fill volumes.[77,78]

Conclusion

Aerosol drug delivery during NIV has gained popularity over the years. Due to many factors that impact drug

Table 1: Optimum technique for aerosol drug delivery with pressurized metered-dose inhalers, jet and mesh nebulizers used during bi-level ventilation

Optimum technique with pMDIs	Optimum technique with jet nebulizers	Optimum technique with mesh nebulizers
Review physician order and identify patient	Review physician order and identify patient	Review physician order and identify patient
Assess patient for hemodynamic status, patient-ventilator synchrony, mask fit, and tolerability	Assess patient for hemodynamic status, patient-ventilator synchrony, mask fit, and tolerability	Assess patient for hemodynamic status, patient-ventilator synchrony, mask fit, and tolerability
Minimize leaks in the mask or circuit	Minimize leaks in the mask or circuit	Minimize leaks in the mask or circuit
Shake pMDI and prime if not used within 24 h	Fill the jet nebulizer between 5 and 6 mL and assemble the jet nebulizer	Assemble the mesh nebulizer based on manufacturer's instructions
Place chamber shaped spacer between the circuit and mask	Place the nebulizer upright between the circuit and mask	Pour the medication into the nebulizer cup
Set the EPAP or CPAP at 5 cm H_2O and IPAP at 10–15 cm H_2O	Set the EPAP or CPAP at 5 cm H_2O and IPAP at 10–15 cm H_2O	Place the nebulizer upright between the circuit and mask
Shake pMDI and place it in the spacer	Operate the jet nebulizer with gas flow of 6–8 L/min	Set the EPAP or CPAP at 5 cm H_2O and IPAP at 10–15 cm H_2O
Actuate the pMDI with the beginning of inspiration	Tap nebulizer periodically during aerosol therapy	Attach the nebulizer to a power source and turn on the power
Wait at least 15 s between actuations. Administer total dose	Continue therapy until the jet nebulizer sputters	Continue therapy until the end of nebulization
Monitor patient to assess clinical response	Monitor patient to assess clinical response	Monitor patient to assess clinical response
Remove the pMDI	Remove the jet nebulizer	Remove the mesh nebulizer
Observe patient for any adverse effects	Observe patient for any adverse effects	Observe patient for any adverse effects
Document clinical outcome	Document clinical outcome	Document clinical outcome

pMDIs: Pressurized metered-dose inhalers, IPAP: İnspiratory positive airway pressure, CPAP: Continuous positive airway pressure, EPAP: Expiratory positive airway pressure

delivery to patients receiving NIV, aerosol therapy in this patient population can be extremely complex. However, if clinicians know what to use, how to use it and why, aerosol therapy can be feasible and effective during NIV.

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Conflicts of interest

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