



Inhalation therapy in mechanical ventilation

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INTRODUCTION

Patients with obstructive lung disease, such as COPD and bronchial asthma, often require ventilatory support via invasive mechanical ventilation (MV) or noninvasive MV (NIMV), depending on the severity of the exacerbation. Many such patients have increased airway resistance and, consequently, airway obstruction, which results in increased positive end-expiratory pressure (PEEP) and, consequently, auto-PEEP (also known as dynamic hyperinflation). Auto-PEEP results in increased respiratory effort, contributing to muscle fatigue in such patients.⁽¹⁾ Therefore, the use of positive pressure MV can improve respiratory function, improving the outcomes of decompensated patients.⁽²⁾ The use of inhaled bronchodilators can significantly reduce airway resistance, contributing to the improvement of respiratory mechanics and patient-ventilator synchrony.

The major advantages of using inhalation therapy in such patients are selective treatment of the lungs and high drug concentrations in the airways. In addition, inhaled drugs have a more rapid onset of action and fewer systemic adverse effects than do drugs administered by other routes. However, correct inhaler technique and regular medication use are needed in order to improve drug efficacy, given that inhaled drugs have shorter half-lives.

In a recently published study, physician practices regarding the prescription of inhaled drugs were analyzed in 70 countries.⁽²⁾ Of the 854 intensivists whose responses

ABSTRACT

Patients with obstructive lung disease often require ventilatory support via invasive or noninvasive mechanical ventilation, depending on the severity of the exacerbation. The use of inhaled bronchodilators can significantly reduce airway resistance, contributing to the improvement of respiratory mechanics and patient-ventilator synchrony. Although various studies have been published on this topic, little is known about the effectiveness of the bronchodilators routinely prescribed for patients on mechanical ventilation or about the deposition of those drugs throughout the lungs. The inhaled bronchodilators most commonly used in ICUs are beta adrenergic agonists and anticholinergics. Various factors might influence the effect of bronchodilators, including ventilation mode, position of the spacer in the circuit, tube size, formulation, drug dose, severity of the disease, and patient-ventilator synchrony. Knowledge of the pharmacological properties of bronchodilators and the appropriate techniques for their administration is fundamental to optimizing the treatment of these patients.

Keywords: Bronchial hyperreactivity; Drug delivery systems; Respiration, artificial.

were analyzed, 99% reported prescribing aerosol therapy to patients on MV, including those on NIMV, and 43% exclusively used nebulizers. During nebulization, ventilator settings were never changed by 77% of the respondents; in addition, 87% stated that ultrasonic nebulizers were superior to jet nebulizers. The aforementioned study provides evidence of the heterogeneity in prescribing inhaled drugs, showing that current scientific knowledge is poorly applied.

Although various studies have been published on this topic, little is known about the efficacy of the bronchodilators routinely prescribed for patients on MV or about the deposition of those drugs throughout the lungs. The use of inhaled drugs in patients requiring NIMV poses an even greater challenge.

INHALATION THERAPY DURING MV

The use of inhaled drugs has the advantage of allowing selective treatment of the lungs by delivering high drug concentrations to the airways, having a rapid onset of action and few systemic adverse effects. It is believed that the beneficial effects of inhaled drugs are smaller in patients on MV than in those breathing spontaneously. In an early study, only 2.9% of the administered dose reached the distal airway (vs. 11.9% when the dose was administered without an artificial airway)⁽³⁾; this might be due to a substantial drug loss caused by the turbulent flow produced by the respiratory prosthesis. However, precautions observed at the time of drug

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administration can improve lung drug deposition,⁽⁴⁾ as shown in Chart 1.

With regard to aerosol delivery devices, it was initially believed that lung drug deposition was better with the use of metered dose inhalers (MDIs) than with the use of conventional nebulizers.⁽⁵⁾ However, when the two types of devices are used correctly, the results are similar.^(6,7) In general, MDIs are more economical and pose a lower risk of nosocomial pneumonia.^(4,7) Clinical studies have shown that nebulizers and MDIs have similar effects on lung function, both types of devices resulting in equivalent changes in FEV₁.⁽⁶⁾

Bronchodilators, corticosteroids, antibiotics, prostaglandins, nitric oxide, anticoagulants, and heliox can be administered via inhalation. However, inhalation is most commonly used for bronchodilator administration, improving ventilatory parameters and patient-ventilator synchrony in cases of airway constriction.⁽⁸⁾ Bronchodilators relax airway smooth muscles, reversing airway obstruction and preventing bronchoconstriction.⁽⁶⁾ Ventilator-dependent patients, COPD patients, and asthma patients routinely receive treatment with inhaled bronchodilators.

PHARMACOLOGICAL AGENTS

The inhaled bronchodilators that are most commonly used in the ICU are beta adrenergic agonists and anticholinergics.⁽⁸⁾ Beta adrenergic agonists can also be administered intravenously, subcutaneously, or orally; however, inhalation is the preferred route of administration because of direct lung delivery, need for a lower dose, rapid onset of action, and reduced systemic absorption, thus reducing adverse effects.^(6,8,9) One study evaluated the emergency room treatment of patients with asthma and showed that there is no evidence to support the use of intravenous β_2 agonists, even in patients refractory to inhaled β_2 agonists.⁽¹⁰⁾ Chart 2 shows the inhaled bronchodilators that are most commonly used in the ICU, including doses and pharmacological characteristics such as onset of action, time to peak effect, and duration of action.

CLINICAL USE OF BRONCHODILATORS

In patients with COPD, long-acting β_2 agonists and inhaled corticosteroids are used in order to relieve symptoms, improve quality of life, improve lung function, and prevent decompensation.⁽⁸⁾ In patients with exacerbation of COPD or severe asthma, emergency bronchodilator treatment is required. The drug of choice is a short-acting β_2 agonist (e.g., albuterol), because short-acting β_2 agonists have a more rapid onset of action and a greater bronchodilator effect and because they can be repeated at short intervals during bronchospasm attacks.⁽⁶⁾ The need for high doses in critically ill patients has led to studies of continuous nebulization in selected patients. However, the results are conflicting, showing no evidence that this strategy is beneficial.^(6,11)

In general, the severity of asthma or COPD exacerbation can be best evaluated by the severity of the attack and the bronchodilator response than by previous lung function.

FACTORS THAT INFLUENCE INHALED DRUG DELIVERY DURING MV

In patients on MV, bronchodilators can be delivered by jet nebulizers, ultrasonic nebulizers, or MDIs. In the case of jet nebulizers, compressed gas generates aerosol particles that are delivered with tidal volume. This necessarily increases the tidal volume delivered in each inspiratory cycle. Ultrasonic nebulizers are available for certain ventilators. They deliver medicine by using high-frequency vibrations to convert the liquid into an aerosol and do not increase patient tidal volume during inhalation.

To date, no clinical differences have been found between jet and ultrasonic nebulizers.⁽⁶⁾ The disadvantages of conventional nebulizers include the need for an external flow source independent of the ventilator, the need to install the equipment, and the need for thorough cleaning. Ultrasonic nebulizers can provide a higher nebulization rate in a shorter period of time; however, their availability is limited by high cost.⁽⁶⁾

Studies investigating clinical differences between nebulizers and MDIs have yielded inconsistent results. The efficacy of MDI-delivered drugs depends particularly on the position of the tube in the ventilator circuit. In the case of MDI-delivered bronchodilators, a spacer is essential and can increase aerosol deposition in the airways by four to six times.⁽¹²⁻¹⁴⁾ A variety of spacers are available. It is currently believed that an MDI with a spacer is as effective as a nebulizer, being more practical and quicker to administer and requiring no disconnection from the ventilator circuit after each dose.

Many other factors influence aerosol deposition in the lower airways, as shown in Chart 3. Such factors include drug-related properties (including physical and chemical properties), the characteristics of the aerosol generator, the position of the aerosol generator in the ventilator circuit, ventilator settings, ventilation modes, heating and humidification of the inhaled air, the characteristics of the endotracheal tube, the anatomy of the airways, and the presence of respiratory secretions.⁽¹⁵⁻¹⁷⁾

Even in ventilator-dependent patients, bronchodilators should preferentially be administered with the head of the bed elevated, given that the sitting position improves drug delivery.⁽¹⁵⁾ Heating and humidification of the inhaled air are required during ventilatory support in order to reduce the risk of ventilator-associated pneumonia. However, they increase particle impaction in the ventilator circuit, reducing aerosol deposition in the more distal airways by as much as 40%.^(12,13)

The aerosol generator should be placed at a distance of 20-30 cm from the endotracheal tube, between the tube and the Y-piece of the ventilator circuit,^(16,18,19) as shown in Figure 1. This is due to the fact that the

Chart 1. Strategies to improve lung drug deposition during mechanical ventilation.

Ventilator-related strategies
Deliver a tidal volume > 500 mL ^a
Maintain an inspiratory flow of 30-50 L/min
Avoid delays between actuation and inhalation
Circuit-related strategies
Remove the filter or deliver the drug at a location more proximal to the filter
Turn the humidifier off 10 min before aerosol delivery
Install the aerosol generator 15 cm proximal to the Y-piece
Device-related strategies
Metered dose inhaler
Heat it and shake it before actuation
Use an appropriate connector
Use a spacer
Coordinate actuation with inhalation
Nebulizer
Use an intermittent-flow nebulizer system only if the gas source is > 15 psi
If an external flow source is used, use a flow rate of 6-8 L/min
Complete the volume by adding 2.5 mL of saline solution

psi: pound-force per square inch. ^aIn patients with obstructive lung disease, a tidal volume > 500 mL can result in auto-PEEP (dynamic hyperinflation). In such cases, respiratory mechanics should be monitored, tidal volume being controlled in order to avoid barotrauma.

Chart 2. Doses and duration of action of the inhaled bronchodilators most commonly administered to patients on mechanical ventilation.

Drug	Formulation	Dose	Onset of action, min	Time to peak effect, min	Frequency of use, number of times/day
β_2 agonist					
Fenoterol hydrobromide	Solution: 5 mg/mL	5-8 drops	5-10	15	3-6
	Aerosol: 100 μ g/jet	1 jet every 5 min			
Albuterol	Aerosol: 100 μ g/jet	2 jets	5-15	30-60	4-6
Anticholinergic agent					
Ipratropium bromide	Solution: 0.25 mg/mL	20-40 drops	15	90-120	4-6
	Aerosol: 20 μ g/jet	4 jets			

inspiratory limb of the ventilator circuit acts as an aerosol reservoir during exhalation.⁽¹⁹⁾ Synchronization of actuation with the beginning of inhalation increases lung drug deposition by as much as 30% when compared with failure to synchronize actuations with inhalation. A delay of 1-1.5 s between actuation and inhalation can reduce the efficacy of drug delivery.⁽¹³⁾

Ventilator settings also play an important role in inhaled drug delivery. A tidal volume of at least 500 mL,⁽²⁰⁾ increased inspiratory time, and low inspiratory flow (30-50 L/min) are recommended in order to optimize lung drug deposition.^(16,18,20) Attention should be paid to the adverse effects of high (> 500 mL) tidal volume in patients with obstructive lung disease, given that it can worsen dynamic hyperinflation or cause barotrauma. According to the authors of an in vitro study, drug delivery by nebulizers can vary depending on the ventilation mode (i.e., pressure-controlled ventilation or volume-controlled ventilation).⁽²¹⁾ However, there have been no clinical studies showing the beneficial effects of any particular ventilation mode on inhaled drug delivery.⁽⁶⁾

High and turbulent flows can increase particle impaction, increasing particle deposition in the proximal airways.⁽¹⁷⁾ The density of the inhaled gas also influences drug delivery. Inhalation of a less dense gas, such as a 70/30 mixture of helium and oxygen, makes airflow less turbulent and more laminar, facilitating inhaled drug delivery.^(22,23)

BRONCHODILATOR RESPONSE DURING MV

Given that it is impossible to assess FEV₁ and FVC in patients on MV, treatment response is evaluated on the basis of respiratory mechanics parameters. Treatment is aimed at reducing inspiratory airway resistance. Reduced inspiratory airway resistance can be confirmed by a reduction in peak pressure or in the difference between peak and plateau pressures during an inspiratory pause. A reduction of more than 10% in the variation in resistance indicates a significant bronchodilator response.⁽⁶⁾ It is important to analyze pre- and post-bronchodilator flow curves, which can

Chart 3. Factors influencing aerosol deposition in the airways during mechanical ventilation.

Factors	Parameters	Influence on aerosol deposition
Ventilator-related	Ventilation mode	In vitro studies have shown that aerosol deposition varies depending on the ventilation mode. A longer inspiratory time translates to better drug delivery.
	Tidal volume	
	Respiratory rate	
	Inspiratory/expiratory time ratio	
	Inspiratory flow	
Circuit-related	Inspiratory trigger	A larger tube translates to a more turbulent flow and worse drug delivery.
	Endotracheal tube size	
	Inhaled gas humidity	
Nebulizer-related	Inhaled gas density	High, turbulent flows increase drug deposition in the proximal airways, thus reducing drug efficacy.
	Nebulizer type	
	Inhaled volume	
	Gas flow	
	Nebulization cycling: inspiratory vs. continuous	
Metered dose inhaler-related	Duration of nebulization	Failure to coordinate actuation with inhalation results in lower lung drug deposition.
	Position in the ventilator circuit	
	Type of spacer and connector	
	Position of the spacer	
Drug-related	Coordination of actuation with inhalation	During mechanical ventilation, higher doses of inhaled bronchodilators are required.
	Type of metered dose inhaler	
	Dose	
	Formulation	
Patient-related	Aerosol particle size	Severe airway obstruction and auto-PEEP reduce deposition of bronchodilators in the more distal airways, thus reducing drug efficacy.
	Duration of action	
	Severity of airway obstruction	
	Mechanism of airway obstruction	
	Dynamic hyperinflation	
	Patient-ventilator synchrony	

 Adapted from Dhand.⁽¹⁵⁾

show a reduction in intrinsic PEEP, i.e., a reduction in auto-PEEP.⁽⁶⁾

BRONCHODILATOR THERAPY DURING NIMV

Given the scientific evidence for the use of NIMV in patients with COPD or asthma, it is necessary to study bronchodilator administration during NIMV. Currently, in daily practice, for bronchodilator administration in patients on NIMV, the mask is removed and the drug is delivered as usual (i.e., by a nebulizer or MDI), or the device is connected to the mask or the ventilator circuit. There is currently no commercially available system designed specifically for inhalation therapy during NIMV.⁽²⁴⁾

As is the case with invasive MV, the effect of the inhaled drug during NIMV depends on the pharmacological properties of the drug and on lung drug deposition. For better drug delivery, aerosol particles must be small enough to penetrate through the upper airways but large enough to avoid being eliminated by the expiratory flow. Devices that produce aerosols with mass of less than 2 µm are more efficient for pulmonary deposition during NIMV.⁽¹⁷⁾

In NIMV-dependent patients, an MDI with a spacer was found to be four to six times more efficient for

bronchodilator administration than an MDI without a spacer.⁽¹⁷⁾ Nava et al.⁽²⁵⁾ evaluated MDI-delivered albuterol in clinically stable COPD patients who were on NIMV and in those who were not. The authors found a significant increase in FEV₁ after albuterol administration, regardless of the method used.⁽²⁵⁾

Aerosol deposition in the mask and nasal cavity significantly reduces lung drug deposition,^(17,26-28) possibly reducing drug efficacy. However, a mask is required for ventilatory support in some patients with bronchospasm, in whom it can avoid intubation.⁽²⁹⁻³²⁾ For increased efficacy, the mask must be well secured. Leaks can significantly reduce drug delivery.⁽³³⁾

Ventilators specifically designed for NIMV have a single-limb circuit, and exhalation valve position can influence the efficiency of aerosol delivery; this does not occur when an MDI is used.⁽¹⁷⁾ Branconnier & Hess⁽³⁴⁾ used an experimental model in which the leak port was incorporated either into the circuit or into the mask in order to determine whether albuterol delivered during NIMV was affected by the use of a nebulizer or an MDI. The authors found that, with the nebulizer, significantly more albuterol was delivered when the leak port was in the circuit than when it was in the mask.⁽³⁴⁾ Calvert et al.⁽³⁵⁾ reported that albuterol delivery was more efficient when the nebulizer was placed between



Figure 1. The aerosol generator should be placed at a distance of 20-30 cm from the endotracheal tube, between the tube and the Y-piece of the ventilator circuit.

the exhalation port and the ventilator for NIMV than when the nebulizer was placed between the exhalation port and the mask. In contrast, Abdelrahim et al.⁽³⁶⁾ observed higher aerosol deposition when the nebulizer was placed between the exhalation port and the mask. The divergent results show that this is a controversial issue and indicate the need for further studies.

The position of the nebulizer in relation to the mask also plays an important role in aerosol deposition, front-loaded nebulizers being more efficient than bottom-loaded nebulizers in delivering drug to the patient.⁽³⁷⁾ An in vitro study investigating the effect of ventilator settings and nebulizer position on albuterol delivery during NIMV showed that albuterol delivery varied significantly depending on nebulizer position in the ventilator circuit, inspiratory/expiratory pressure levels, and respiratory rate. Albuterol delivery was

greatest (with as much as 25% of the nominal dose being delivered) when the nebulizer was placed between the mask and the circuit, when inspiratory pressure was highest (20 cmH₂O), and when expiratory pressure was lowest (5 cmH₂O).⁽³⁸⁾

The extent of lung disease and the ability of patients to tolerate the mask also play a decisive role in the success of treatment with NIMV and inhalation therapy. Patient-ventilator synchrony improves lung drug deposition. A delay of 1-1.5 s between device actuation and the beginning of inhalation can significantly reduce the efficiency of drug delivery.^(13,17)

FINAL CONSIDERATIONS

Many patients with COPD require ventilatory support via invasive MV or NIMV. Inhaled drug delivery is complex in this context. Multiple factors influence the efficacy of inhaled bronchodilators administered during MV. For improved drug efficacy, the appropriate dose and formulation should be prescribed. Measures that can improve the efficacy of bronchodilators include the use of a spacer, patient-ventilator synchrony, an appropriate interval between doses, and adjustment of the ventilator settings during administration.

Despite the recommendations for inhaled drug delivery, few such interventions are implemented in daily clinical practice. Knowledge of the factors influencing lung drug deposition is fundamental to optimizing the treatment of these patients.

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