Factors affecting bronchodilator delivery in mechanically ventilated adults

Arzu Ari and James B Fink

ABSTRACT

Background: Bronchodilators are increasingly being used in patients undergoing mechanical ventilation. There are multiple factors that affect bronchodilator delivery during mechanical ventilation. These factors can be classified into three categories: ventilator-related factors, circuit-related factors and device-related factors.

Aims: The purpose of this paper is to review in depth each of the factors affecting bronchodilator delivery during mechanical ventilation.

Search strategies: A literature search was undertaken using several databases including Cochrane, Pubmed, Medline, Cinahl and Science Direct. The literature search, although limited to the English language, covered materials from 1985 to May 2009.

Conclusion: Aerosolized bronchodilator delivery to mechanically ventilated patients is complex as a result of the multiple factors that affect the amount of aerosol deposited in the lower respiratory tract. When these factors are not carefully controlled and the optimum technique for aerosol delivery is not utilized, a greater proportion of the aerosol will deposit in the ventilator circuits and artificial airways decreasing the available dose to the patient. Attention to these factors and optimizing aerosol delivery techniques will help to reach therapeutic endpoints of bronchodilator therapy in patients receiving ventilatory support.

Relevance to clinical practice: Bronchodilator delivery during mechanical ventilation is factor and technique dependent. A clear understanding of the factors affecting aerosol drug delivery during mechanical ventilation is very important in optimizing the efficiency of bronchodilator delivery in mechanically ventilated adults. Through the recommendations made in this paper, clinicians will be able to optimize both their technique and the therapeutic outcomes of aerosol drug delivery in patients receiving ventilator support.

Key words: Aerosol deposition • Bronchodilator • Drug delivery • Mechanical ventilation • Nebulizer • pMDI • Ventilator

INTRODUCTION

Inhaled bronchodilators are commonly administered to adults undergoing mechanical ventilation to relieve dyspnea and reverse bronchoconstriction. However, there are several factors that affect bronchodilator delivery during mechanical ventilation. These factors can be classified into three categories: ventilator-related factors, circuit-related factors and device-related factors. The lack of attention and knowledge given to these factors not only creates a significant proportion of the aerosol depositing in the ventilator circuits and artificial airways but also decreases the efficiency of aerosol drug delivery. The purpose of this paper is to review the factors affecting bronchodilator delivery during mechanical ventilation and provide insights for optimizing aerosol delivery in these patients.

Authors: Dr A Ari, PhD, RRT, PT, CPFT, Assistant Professor, Division of Respiratory Therapy, School of Health Professions, College of Health and Human Sciences, Georgia State University, Atlanta, GA 30302-4019, USA; JB Fink, Adjunct Professor, Division of Respiratory Therapy, School of Health Professions, Georgia State University, Atlanta, GA 30302-4019, USA
Address for correspondence: A Ari, Division of Respiratory Therapy, School of Health Professions, College of Health and Human Sciences, Georgia State University, P.O. Box 4019, Georgia 30302-4019, USA
E-mail: aari1@gsu.edu; arzuari@hotmail.com

SEARCH STRATEGY

The studies reviewed in this paper were derived from searches of bibliographic databases including Cochrane, Pubmed, Medline, Cinahl and ScienceDirect. In order to combine terms relating factors affecting bronchodilator administration in adults, a broad search strategy was used (see Figure 1). Search terms used for this review are 'bronchodilators or beta-agonist' and 'mechanical ventilation or mechanical ventilator' and 'aerosol devices or nebulizers or metered-dose inhalers' and 'adults'. Both *in vitro* and clinical trials in English were chosen. Studies published in foreign languages were excluded because of lack of translations. The search identified 77 articles. The selection criteria consisted of *in vitro* and clinical trials involving

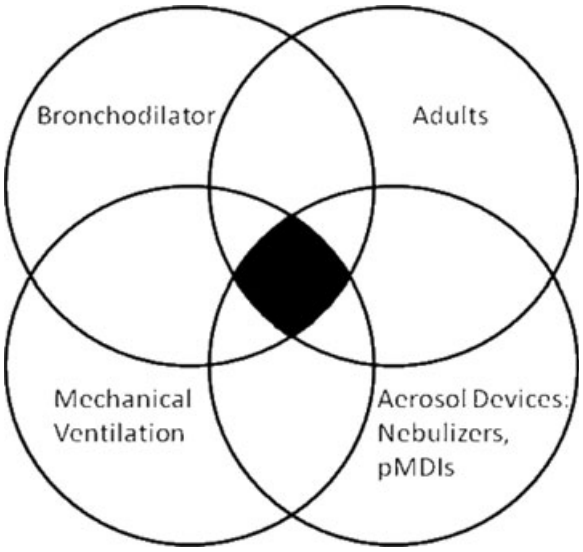

Figure 1 Studies selected for this paper included dose overlapping (illustrated by shaded area) bronchodilator, mechanical ventilation, aerosol devices and adults.

adult patients on mechanical ventilators who were given bronchodilators. The exclusion criteria included the non-relevant topics, populations, interventions and outcomes. The authors also reviewed the reference lists of all relevant studies to include findings from more studies and hand searched respiratory journals as well as meeting abstracts in an effort to include all available primary studies. This review covers 53 citations in the literature published from 1985 to May 2009 and is divided into three categories: ventilator-related, circuit-related and device-related factors.

VENTILATOR-RELATED FACTORS

Several studies have investigated the effect of ventilator-related factors in aerosol deposition during mechanical ventilation. The mode of ventilation, tidal volume, inspiratory time, duty cycle, flow bias flow (breath-triggering mechanism) and inspiratory waveform all influence aerosol delivery to mechanically ventilated patients (O'Riordan *et al*., 1994; Fink *et al*., 1996, 1999; Hess *et al*., 2003; Dolovich *et al*., 2005; Ari *et al*., 2010a; Guerin *et al*., 2008).

Mode of ventilation

Ventilator mode significantly influences aerosol drug delivery to the lower airways. Fink *et al*. (1996) determined the effect of ventilator mode on albuterol delivery from a pressurized metered-dose inhaler (pMDI) with spacer chamber in an *in vitro* model of adult ventilation. They compared controlled mechanical ventilation (CMV), assist control (AC), pressure control (PC) and continuous positive airway pressure (CPAP), with a range of conditions. For example, with a tidal volume of 800 mL and a dry ventilator circuit deposition efficiency was similar in CMV, AC and PC (30%, 31.9% and 30.9%, respectively) and was greater with CPAP (39.2%). Utilizing a given ventilator's spontaneous mode, such as CPAP increased aerosol delivery by up to 30% compared with controlled mechanical breaths at equivalent tidal volumes (Fink *et al*., 1996). Hess *et al*. (2003) evaluated delivery of albuterol from pMDI with spacer (four puffs) and jet nebulizer (JN) (4-mL fill volume) in volume control ventilation (VCV) or pressure control ventilation (PCV), to deliver tidal volume of 600 mL, a respiratory rate of 15/min, and a positive end expiratory pressure (PEEP) of 5-cm H_2O. Inspiratory times of 1 and 2 s were compared with low compliance/low resistance and high compliance/high resistance test lung settings. Deposition by pMDI was the same regardless of which mechanical ventilation mode, inspiratory time and lung settings used. The efficiency of nebulizers varied across conditions. Delivery in VCV was similar across lung settings, and more than twofold greater with 2 s inspiratory time. Delivery in PCV was twofold greater than VCV at 1 s in high compliance/high resistance, and similar at 2 s, but significantly less under low compliance/low resistance conditions (Hess *et al*., 2003).

Tidal volume

In order to achieve optimum aerosol drug deposition to the lower respiratory tract, the tidal volume of the ventilator should be larger than the volume of ventilator tubing and the endotracheal tube (ETT) between the nebulizer and the patient. For example, if the nebulizer is placed in the inspiratory limb of the ventilator circuit, 6 inches from the Y, the aggregate volume of tubing, Y and ETT may be as high as 150 mL. A tidal volume greater than 200 mL would deliver aerosol collected in the nebulizer and tubing and allow an additional volume of 50 mL to 'chase' the aerosol down the ETT into the lungs. Setting the tidal volume at greater than 500 mL in an adult model was shown to improve aerosol drug delivery from a pMDI distal to the ETT (lower respiratory tract) (Fink *et al*., 1996, 2009). Despite this, it is important to remember that large tidal volumes (greater than 8–10 mL/kg) can cause volutrauma and should not be used just to increase aerosol deposition efficiency. (Guerin *et al*., 2008).

Inspiratory time and duty cycle

Duty cycle is the ratio of inspiratory time to total breathing cycle time (Ti/Ttot). As duty cycle increases,

aerosol delivery through the ETT increases, independent of the type of aerosol generator (O'Riordan *et al*., 1994; Fink *et al*., 1996, 1999). This is intuitively obvious in the case of nebulizers, which generate aerosol continuously, in that the greater the proportion of inspiratory time, the larger proportion of aerosol would be inhaled. However, it is less obvious in the case of pMDIs, which generate aerosol over a very short period of time. Using a pMDI in an *in vitro* model, Fink *et al*. (1996) compared the effect of duty cycle (0.25 and 0.5) and inspiratory flow (40 and 80 L/min) on aerosol delivery in mechanically ventilated patients. Although drug delivery increased significantly with the increase in duty cycle, a much greater increase occurred with inspiratory flow of 40 L/min versus 80 L/min (Fink *et al*., 1996). Therefore, using a duty cycle equal or greater than 0.30 is recommended, while minimizing the degree of intrinsic PEEP (Dhand, 2008; Guerin *et al*., 2008).

Flow

Because higher inspiratory flow rates increase turbulence and the inertial impaction of aerosol particles, lower inspiratory flows improve aerosol delivery in mechanically ventilated patients (Manthous *et al*., 1995; Fink *et al*., 1996; Dhand, 2003).

Therefore, peak inspiratory flow rates should be reduced as much as is practically tolerable (Fink *et al*., 1999; Fink, 2009). Fink *et al*. (1999) reconciled *in vitro* and *in vivo* measurements of aerosol delivery from a pMDI in mechanically ventilated patients. After testing 10 mechanically ventilated patients and concluding the accuracy of *in vitro* model in reflecting *in vivo* delivery, they studied the effect of flow rate (40 versus 80 L/min) on aerosol delivery in patients receiving ventilatory support and demonstrated greater than twofold increase in aerosol delivery from a pMDI with peak inspiratory flows of 40 versus 80 L/min. When in doubt, one should use slow flow rates (Dhand, 2003). Although an inspiratory flow of 30–50 L/min can be used to optimize aerosol bronchodilator delivery during mechanical ventilation, it is also important to minimize the intrinsic PEEP (Guerin *et al*., 2008).

Bias flow (breath-triggering mechanism)

Many modern ventilators utilize continuous trigger or bias flow through the ventilator circuit to reduce patient work of breathing. Flow-triggered ventilation negatively affects nebulizers as it dilutes the aerosol and increases the washout of the aerosol into the expiratory limb between breaths. However, it is important to emphasize that properly synchronized actuation of pMDI was not impacted by flow trigger (Fink *et al*., 1996).

Ari *et al*. (2010a) determined the influence of bias flow with a jet (JN) and vibrating mesh (VM) nebulizer on albuterol sulfate delivery in a model of adult mechanical ventilation using ventilator settings of Vt 500 mL, respiratory rate (RR) 20/min, peak inspiratory flow (PIF) 60 L/min, Descending waveform and PEEP 5-cm H_2O. A ventilator with a heated humidifier and 15-mm ID heated wire ventilator circuit delivered adult settings through an 8-mm ID ETT to an absolute filter attached to a test lung at bias flows of 2 and 5 L/min. Albuterol sulfate (2.5 mg) was nebulized in each condition, eluted from the filter and analysed by spectrophotometry. They reported increasing bias flows through the ventilator circuit decreased the amount of aerosol deposited and lower bias flow (equal to or less than 2 L/min) is recommended for greater aerosol delivery with continuous nebulizers (Ari *et al*., 2010a).

Inspiratory waveform

Inspiratory waveform influences aerosol drug delivery in mechanically ventilated patients. Square wave flow patterns deliver less aerosol than sinusoidal or descending ramp waveforms. This may be as a result of the sudden onset and duration of peak flows, and the associated turbulence. Waveform has more influence on nebulizer efficiency than on pMDI efficiency. Hess *et al*. (2003) evaluated the effect of inspiratory flow patterns (constant versus descending), using an *in vitro* lung model. At inspiratory flows less than 36 L/min, they reported differences between flow patterns with pneumatic nebulizer but not pMDI (Hess *et al*., 2003). It appears that the greater the PIF the greater the impact of waveform on aerosol delivery with nebulizers and pMDI.

CIRCUIT-RELATED FACTORS

Endotracheal tube

The ETT influences aerosol deposition during mechanical ventilation. Crogan and Bishop (1989) studied the efficiency of metaproterenol administration when delivered via an ETT using a pMDI and found that aerosol delivery to the filter decreased with reduction of the inner diameter of the ETT. For instance, the percentage of drug exiting the ETT was 3% for a 6.0-mm ETT, whereas it was 6.5% for a 9.0-mm ETT (Crogan and Bishop, 1989). Another study (Takaya *et al*., 2002) compared the delivery efficiency of aerosols administered through five different ETTs with an internal diameter of 5–7.5 mm. In addition, they concluded that delivery efficiency was significantly lower in the smaller-sized ETT. ETTs are narrower than the trachea and their smooth interior surfaces create a more laminar flow path than do the structures of the upper airway

(Dhand, 2000; Fink, 2009). Therefore, aerosol drug deposition is reduced as the lumen of ETT decreases (Crogan and Bishop, 1989; Takaya *et al*., 2002). This is especially true in the case of pediatric artificial airways (Ahrens *et al*., 1986; Bishop *et al*., 1990). Takaya *et al*. (2002) studied the efficiency of bronchodilator delivery through five different ETTs with an internal diameter of 4–8.5 mm. They reported that bronchodilator efficiency with ETT was decreased with a connector of 15 mm that was attached to the ETT (Takaya *et al*., 2002). In addition, O'Riordan *et al*. (1994) found *in vivo* that 2.6 and 7% of nebulizer output deposits in the ETT during inspiration and expiration, respectively.

Aerosol deposition via tracheostomy tubes has not been studied as much as ETT, O'Riordan *et al*. (1994) tested nebulizer delivery to seven mechanically ventilated patients with a tracheostomy under optimal conditions. A radiolabelled aerosol was used filling the nebulizer with 2 mL of saline to dissolve the radiolabelled substance. It was then placed in the inspiratory limb, 12 inches from the Y adaptor. The ventilator nebulizer function was used to deliver aerosol during inspiration only. It was found in a study that approximately 3% of the nominal dose from a nebulizer deposits in the tracheostomy tube rather than reaching the patient's lungs (O'Riordan *et al*., 1994). As biofilm and secretions collect in the ETT, the diameter narrows, resistance increases as well as aerosol losses. Consequently, it is prudent to place the largest diameter ETT that the patient can safely tolerate.

Heat and humidity

Aerosol drug delivery may be reduced by up to 40% when heated/humidified ventilator circuits are used as compared with non-humidified circuits (Fuller *et al*., 1992; O'Riordan *et al*., 1992; Garner *et al*., 1994; Diot *et al*., 1995; Fink *et al*., 1996, 1999). However, the increased efficiency of aerosol delivery must be weighed against the damage of prolonged ventilation with cold dry gasses.

Active heated humidifiers are commonly used during mechanical ventilation of infants and small children, and a substantial proportion of adults. The heat and humidity of an inhaled gas to body temperature pressure standards prevent drying of the airway mucosa, and reduces bronchospastic responses to breathing cold dry air, high absolute humidity in the ventilator circuit reduces aerosol deposition by approximately 40% and increases particle size during mechanical ventilation (Fuller *et al*., 1992; O'Riordan *et al*., 1992; Garner *et al*., 1994; Diot *et al*., 1995; Fink *et al*., 1996, 1999). Although this effect has been well documented in the literature, the causes, and thus possible solutions are less clear. Lower deposition because of heat and humidity may be because of particles experiencing hygroscopic growth that leads to the formation of larger, less absorbable aerosol particles, or it may be caused by loss of those larger particles in the ventilator circuit because of gravity. Even though humidity has an unwanted effect on drug delivery, removing the humidifier is not recommended for routine aerosol therapy as it requires breaking the circuit and waiting several minutes for the circuit to dry (Dhand, 2004).

Lin *et al*. (2009) recently reported that delivery efficiency of albuterol from a pMDI with spacer chamber during mechanical ventilation with a heated wire circuit was not reduced for more than 1 h after turning on the heated humidifier. Reduction of aerosol delivery occurred as substantial condensation formed in the spacer and tubing. After 3 h of humidifier operation, turning off the humidifier for up to 10 min prior to administration of aerosol via pMDI did not improve delivery (Lin *et al*., 2009). For inexpensive drugs, such as salbutamol or ipratropium bromide, increasing the dose may be safer than turning off the humidifier. For more expensive drugs, such as antibiotics, the efficiency advantage of a dry circuit may be cost effective. If a dry ventilator circuit needs to be used for aerosol delivery, the administration of medication should be achieved in a short period (less than 10 min) in order to minimize the effects of dry gas on the airway mucosa (Dhand, 2008).

Heat and moisture exchangers (HMEs) capture the heat and moisture in the exhaled air and transfer part of the heat and humidity to the next inspired breath, providing about 70% absolute humidity at 30°C. The material in the HME acts as filter, presenting a formidable barrier to aerosol delivery. The HME should be removed from between the aerosol device and the patient during administration of medical aerosols and placed back into the circuit after aerosol therapy is completed. Placement of nebulizers between the HME and patient airway may overload the HME with both drug and liquid, and increase work of breathing through the device.

Density of inhaled gas

High inspiratory flow during mechanical ventilation produces turbulence in the narrow airway passages that causes aerosol to deposit on the ventilator circuit and in the artificial airway. Inhaling a helium-oxygen mixture creates the persistence of laminar flows in the airways that may improve aerosol deposition by decreasing particle-impaction losses caused by airflow turbulence (Svartengren *et al*., 1989). Goode *et al*. (2001) identified the effect of helium-oxygen mixture on aerosol delivery from pMDIs and JNs in a bench model of mechanical ventilation. They

showed that an 80/20 helium/oxygen (Heliox) mixture increases aerosol deposition up to 50% when compared with using oxygen by itself when using a pMDI or nebulizer. Aerosol delivery efficiency and gas density in the ventilator circuit are inversely related. The lowest gas density (80/20 helium/oxygen proportion) provides the highest bronchodilator delivery but it also decreases the ability to generate aerosol with a JN (Goode *et al*., 2001). Hess *et al*. (1999) administered different doses of albuterol at various flow rates using oxygen or heliox in order to evaluate the effect of heliox on the performance of conventional and continuous nebulizer. They found that both inhaled mass and particle size reduced significantly for both nebulizers. For instance, inhaled mass with the heliox-driven conventional nebulizer (16%) was lower than that of heliox-driven continuous nebulizer (67%). Because heliox is not as effective in aerosolizing the medication, it should not be used to power the nebulizer (Goode *et al*., 2001; Duarte, 2004). If a helium/oxygen mixture must be used with the nebulizer, flow should be increased by twofold in order to produce comparable aerosol output as air or oxygen (Hess *et al*., 1999; Goode *et al*., 2001). Another strategy in maximizing aerosol deposition with a nebulizer is to power it at 6–8 L/min with oxygen and, then, into an entrainment in the ventilator circuit that contains heliox (Goode *et al*., 2001; Duarte, 2004). Tassaux *et al*. (1999) showed that aerosol deposition to the lower airways is increased by 50% with that method compared with using oxygen by itself in the ventilator circuit. It is important to remember that heliox may adversely affect the function of some ventilators and therefore it must be tested before use in order to prevent detrimental effects on patients (Tassaux, 1999; Guerin, 2008).

Right angle elbow adapter

Many ventilator circuits incorporate a right angle elbow adapter that is placed between the ETT and the 'Y' adapter that connects the inspiratory and expiratory limb of the circuit. Fink *et al*. (1999) reported that the removal of the right angle elbow adapter increased the amount of aerosol delivery from a pMDI on a humidified ventilator circuit but not on a non-humidified circuit. It is unclear whether the efficiency gained by removing the elbow is not lost further down the airway.

DEVICE-RELATED FACTORS

Type of aerosol device used

Inhaled medications can be administered during mechanical ventilation using either a pMDI or nebulizer. Several *in vitro* and *in vivo* studies have been conducted in order to quantify the relative lung deposition efficiencies of different nebulizers and pMDIs. *In vitro* studies indicated that aerosol drug delivery to the lower respiratory tract can vary from 0 to 42% with nebulizers (Fuller *et al*., 1992; O'Doherty *et al*., 1992; O'Riordan *et al*., 1992; Thomas *et al*., 1993; Ari *et al*., 2010a) and ranges from 0.3% to 97.5% with pMDIs (MacIntyre *et al*., 1985; Fuller *et al*., 1990; Rau *et al*., 1992; Taylor *et al*., 1993; Thomas *et al*., 1993; Diot *et al*., 1995; Fink *et al*., 1996, 1999; Ari *et al*., 2010a).

Position of aerosol device in circuit

The location of the aerosol device in the ventilator circuit will significantly affect aerosol drug delivery. Placing the nebulizer farther away from the ETT improves aerosol deposition because the ventilator tubing acts as a spacer in which the aerosol accumulates between breaths (Hughes and Saez, 1987; O'Doherty *et al*., 1992; O'Riordan *et al*., 1992; Thomas *et al*., 1993). Ari *et al*. (2010a) used an *in vitro* model of adult mechanical ventilation, without bias flow, to compare the efficiency of JNs, ultrasonic nebulizers (UN), VM nebulizers (VM) and pMDIs with spacer at three different positions in the ventilator circuit under both dry and humidified conditions. Each type of aerosol generator was placed between the ventilator circuit and ETT (position 1), in the inspiratory limb of the circuit 6 inches from the Y adapter (position 2), or 6 inches from the ventilator (position 3). The VM, UN and pMDI delivered more albuterol in position 2 with both unheated (30.2%, 24.7% and 27.8%, respectively) and heated circuits (16.8%, 16.5% and 17%). In contrast, the JN was most efficient when it was placed proximal to the ventilator under both unheated (14.7%) and heated (6.0%) conditions. It was hypothesized that the continuous output from the JN filled the inspiratory limb of the circuit between inspiration, increasing percent of output delivered with each breath.

Nebulizer-related factors

Three different types of nebulizers are used for aerosol drug delivery during mechanical ventilation: (1) The JN is the historically most common nebulizer that generates aerosol constantly, during inhalation, exhalation and breath hold (Ari *et al*., 2009). (2) The VM nebulizer consists of a vibrational aperture plate which expands and contracts when an electrical current is given. The aperture plate has up to 1000 tapered holes and creates a micro-pumping action in order to produce aerosols through the holes (Dhand, 2004; Ari *et al*., 2009). (3) The UN generates aerosol particles with the high frequency vibrations of a piezoelectric crystal (Ari *et al*., 2009).

Nebulizer type

Not only the type of nebulizer but also the different batches of the same brands of nebulizers produce variability in aerosol deposition in mechanically ventilated patients (Alvine *et al*., 1992; Loffert *et al*., 1994; Hess *et al*., 1996). Alvine *et al*. (1992) studied the frequency of malfunction, variability in rate of nebulization and in particle size of eight disposable JN models. They reported variability of nebulization rate ranging from 57% to 129% within specific models. Loffert *et al*. (1994) tested 17 JNs available on the market. After filling all nebulizers with 2 mL of saline solution and 0.5 mL of albuterol, nebulizers were compared for total output, nebulization time, and percent output in respirable range. Loffert *et al*. found that the output characteristics of commercial nebulizers vary greatly and impact not only nebulization time but also the total amount of drug delivered to the lungs.

Overall, most JNs are less efficient than ultrasonic and VM nebulizers (Harvey *et al*., 1993; Dhand, 2002, 2004; Ari *et al*., 2009, 2010a; Waldrep and Dhand, 2008). Although JNs are less expensive, both ultrasonic and VM nebulizers provide a higher rate of nebulization in a shorter period of time (Ari *et al*., 2010a; Dhand 2002, 2004; Harvey, 1993). Therefore, it is certainly important to characterize the efficiency of a nebulizer before using it to deliver aerosolized drugs to critically ill patients.

Intermittent or continuous nebulization

Nebulizers may be operated continuously by pressurized gas or intermittently by using a synchronized driving pressure and gas flow from the ventilator. Intermittent nebulization is more efficient for aerosol delivery than is continuous nebulization, because it minimizes aerosol loss during exhalation (Hughes and Saez, 1987; Miller *et al*., 2003). Hughes and Saez (1987) evaluated the nebulizer mode and position on dose efficiency during mechanical ventilation. Although nebulizer mode included both intermittent and continuous nebulization, nebulizer positions were: (1) nebulizer placement at the Y and (2) 'Manifold position' in which nebulizer was placed 90 cm from the 'Y' adapter. They found that manifold position offers the patient twofold more medication than does nebulization at the 'Y'. Placing the nebulizer closer to the ventilator may have greater impact on drug delivery than intermittent versus continuous nebulization (Hughes and Saez, 1987).

When nebulization is synchronized with inspiration through mechanical ventilation, its efficiency is enhanced as much as four times more than a continuous nebulization (Miller *et al*., 2003). However, many modern ventilators do not offer synchronized nebulizer options.

Residual (dead) volume

Residual volume (also termed dead volume) is the amount of medication remaining in the nebulizer at the end of a treatment. It can range from 0.1 to 2.4 mL. The greater the dead volume, the less amount of drug is nebulized. JNs do not function well with small fill volumes like 2 mL or less because this is close to residual volume. Small volume UN and VM nebulizers were found to have smaller residual volumes than JNs (Harvey *et al*., 1993; Phillips and Millard, 1994; Dhand, 2008). However these nebulizers are much more expensive than JNs. Because JNs do not aerosolize below dead volume, it is recommended to use a fill volume of 4–5 mL unless the nebulizer is specifically designed for a smaller fill volume (Hess *et al*., 1996). This precaution dilutes the medication, allowing for a greater proportion to be nebulized, although it increases the treatment time.

Gas flow

JNs are designed to operate by means of varied levels of compressed gas flow and pressure. Each model of JN is designed to work best at a specific flow, ranging from 2 to 8 L/min, which should be listed on the device label. Operating any JN at a lower flow or pressure will increase particle size and thereby reduce absorption. For example, a JN designed to operate at 6–8 L/min at 50 psi will produce larger particles if driven by a compressor producing 13 psi (Ari *et al*., 2009). Consequently, JNs should be matched with a compressor or gas source that matches their intended design. Gas flow is also inversely related to nebulization time. Using a higher gas flow rate in aerosol therapy will decrease the amount of treatment time needed to deliver the set amount of drug. Ultrasonic and VM nebulizers are not influenced by gas flow as they are electrically powered nebulizers.

pMDI-related factors

pMDIs are commonly used for administering inhaled drugs to mechanically ventilated patients because they are cost effective, convenient, reliable and safe (Georgopoulos *et al*., 2000). The efficiency of pMDIs is affected by the three factors, pMDI actuation, spacer and shaking the canister.

pMDI actuation

Actuation of a pMDI should be synchronized with the precise onset of inspiration in order to maximize aerosol drug delivery. When a pMDI is actuated into a cylindrical spacer synchronized with inspiration, its efficiency increases approximately 30% when compared with actuation during expiration (Diot *et al*.,

1995). According to Diot *et al*. (1995), failure to synchronize actuations with inspiration reduced inhaled mass by 35% and to pause 1 min between actuations leads to a significant decrease of 72%. Using an *in vitro* model, Everard *et al*. (1995) also studied the effect of pMDI actuations on bronchodilator delivery by not shaking the canister and using multiple rapid actuations. They reported that not shaking the pMDI before use reduced the respirable dose by 35%, and respirable doses delivered by a salbutamol pMDI under various conditions. In addition, the rapid actuation of more than two puffs with the pMDI may cause a reduction in drug delivery caused by turbulence and the coalescence of particles (Everard *et al*., 1995).

Manthous *et al*. (1995) administered 5, 10 and 15 puffs of pMDI albuterol to 10 patients whose resistive airway pressure (peak pressure – pause pressure gradient) of more than 15-cm H_2O during quite breathing on AC ventilation. They found that resistive airway pressure after five puffs reduced in nine of ten patients from 25.1 to 20.8-cm H_2O and giving 10 more puffs to the patients decreased in nine of nine patients from 20.8 to 19.0-cm H_2O. Therefore, they concluded that bronchodilator administration with the pMDI and spacer is effective in doses up to 15 puffs in patients receiving ventilator support.

Spacer

Several spacers with different designs and sizes are available on the market for aerosol drug delivery in mechanically ventilated patients. A study done by Rau *et al*. (1992) tested the efficiency of a reservoir device for pMDIs during mechanical ventilation. In this *in vitro* study, three different models were tested. The first model used a pMDI directly on the endotracheal tube using an actuator adaptor. The second used an inline chamber (Aerovent, Monaghan Medical Corporation, Plattsburgh, NY, USA) placed on the inspiratory limb just before the Y adaptor. The third used the inline chamber placed between the ETT and the Y adaptor. A total of 10 actuations were made each one 30 s apart. The results showed significance among the three methods. The pMDI directly on the ETT delivered 7.3% of the medicine. The method with the reservoir on the inspiratory limb showed a 32.1% deposition, whereas the reservoir placed between the ETT and the Y adaptor showed 29% deposition. The use of a reservoir showed a significant increase in the amount of drug delivered yet the positioning of the reservoir did not show a significant increase statistically ($p > 0.05$) although the reservoir on the inspiratory limb did show a greater deposition.

Harvey *et al*. (1995) described an *in vivo* study that was performed as a comparison with the *in vitro* studies that have already been done to see if the use of a spacer in the patient-ventilator circuit improves aerosol delivery when using a nebulizer. The *in vitro* model showed that aerosol delivery to a test lung was 30% greater with a spacer. For the *in vivo* model, 10 patients were given aerosolized treatments that had been radiolabelled. A gamma camera was used to measure the amount of drug that was deposited in each patient's lungs. Their results showed that the use of a spacer increased lung deposition by 36%. This correlates well with the *in vitro* model.

Using a chamber shaped spacer with the pMDI results in four- to sixfold greater aerosol drug delivery when compared with either an elbow adapter or a unidirectional inline spacer (Rau *et al*., 1992; Fuller *et al*., 1994; Dhand *et al*., 1995). It was also found that the efficiency of a bidirectional inline spacer was higher than the efficiency of an unidirectional inline spacer and achieved comparable efficiency with chamber spacers (Rau *et al*., 1998). Placing the spacer 15 cm from the ETT increases aerosol deposition and creates a more significant bronchodilator response (Dhand *et al*., 1995; Dhand *et al*., 1996; Ari *et al*., 2010b).

Shaking the canister

Not shaking a pMDI canister that has been standing overnight decreases total and respirable dose by as much 25% and 35%, respectively, because the drugs in pMDI formulations are usually separated from the propellants when standing (Everard *et al*., 1995). Therefore, pMDIs must be shaken before the first actuation of each dose administered.

RECOMMENDATIONS FOR BRONCHODILATOR ADMINISTRATION IN MECHANICALLY VENTILATED PATIENTS

Bronchodilator delivery during mechanical ventilation is factor and technique dependent. As discussed above, many factors related to ventilator, circuit and device influence aerosol drug deposition to the lower respiratory tract. When clinicians gain a clear understanding of the factors affecting aerosol drug delivery during mechanical ventilation, they can optimize the process and its therapeutic outcomes in mechanically ventilated adults. Based on a review of the literature, the following recommendations are suggested with the aim of improving bronchodilator delivery for patients receiving ventilatory support.

Recommendations for ventilator settings

Use of low inspiratory flow, tidal volume greater than the circuit volume between nebulizer and patient, duty cycle of 0.3, and decreasing ramp or sinusoidal waveforms will together increase aerosol deposition in mechanically ventilated patients. In addition, spontaneous modes of breathing during mechanical ventilation are recommended, when possible, because they have been proven to be more effective than controlled modes in optimizing bronchodilator delivery.

Recommendations for circuit-related factors

If a heated humidifier is used in mechanically ventilated patients, it should be left on during the administration of aerosol drugs. If the HME is used, it should be removed during treatment so that it is not a barrier between the aerosol device and the ETT. Low density gas like heliox should not be used to power a nebulizer but it can be used to entrain the aerosol into the ventilator circuit and patient. In the latter case, the function of the ventilator must be tested before its use on intensive care unit patients in order to prevent detrimental effects.

Recommendations for device-related factors

When the standard JN is used under normal conditions with heated humidification, aerosol deposition varies between 1% and 3%. This can be increased to 15% if the ventilator settings and other factors are optimized. JNs should be run intermittently, when possible. If

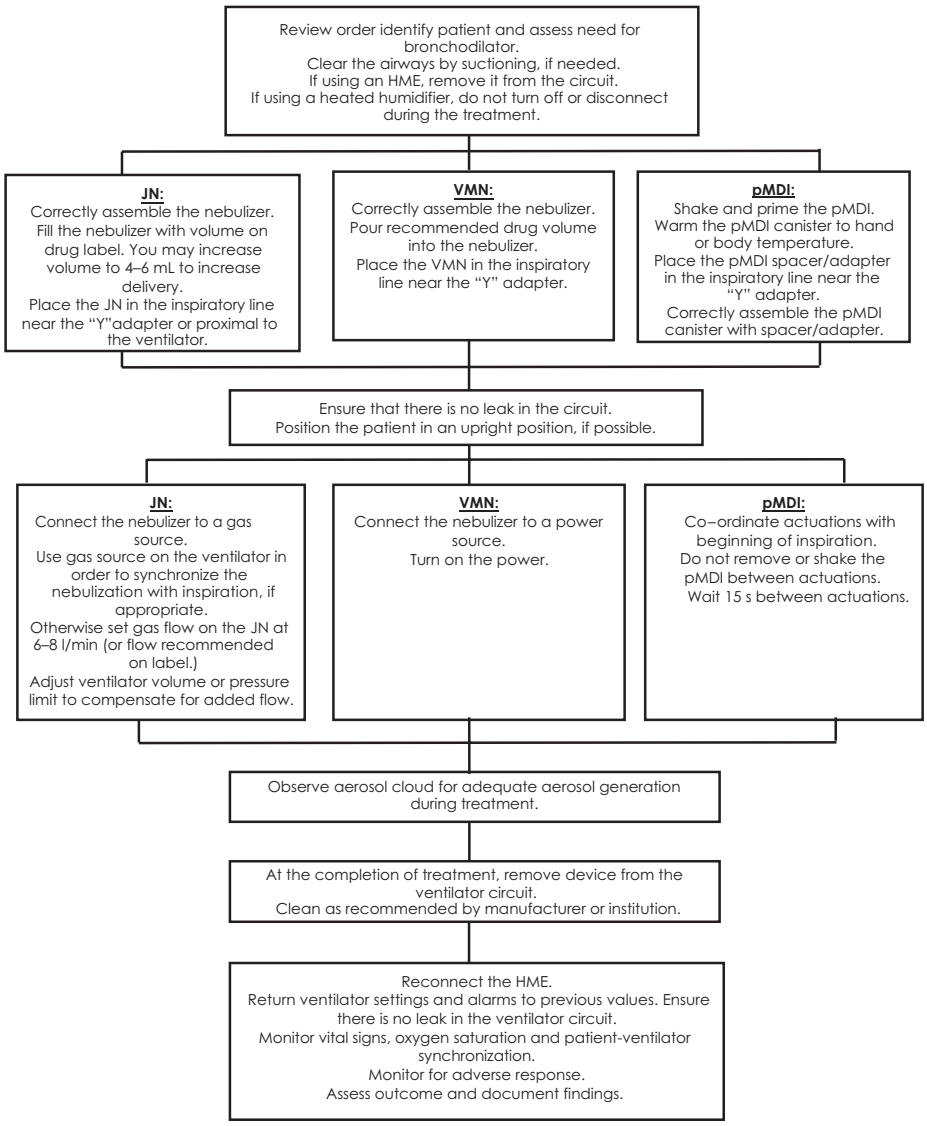

Figure 2 An algorithm describing steps for optimal drug administration technique by each aerosol generator.

they are run continuously, the flow rate should be set at 6–8 L/min and the ventilator parameters such as tidal volume and pressure should be adjusted accordingly. VM nebulizers are a good alternative for bronchodilator delivery in mechanically ventilated patients because aerosol deposition with UN and VM nebulizers is more than 10% without the addition of gas into the ventilator circuit. The JN was most efficient when placed closer to the ventilator. However, other aerosol devices like the VM nebulizer, UN and pMDI that do not add flow into the ventilator circuit were more efficient when placed 6 inches from the

Table 1 Ventilator-related factors, their effects and recommendations to optimize bronchodilator delivery in mechanically ventilated adults

Factors	Effects	Recommendations
Mode of ventilation	The efficiency of nebulizer is lower in pressure-controlled ventilation than in volume-controlled ventilation in patients with low compliance and low resistance.	Prefer volume-controlled ventilation when using a nebulizer, in patients with low compliance and low resistance if possible.
	Spontaneous modes such as continuous positive airway pressure increase aerosol drug delivery up to 23%.	Use spontaneous modes, if tolerable by patients.
Tidal volume	Low tidal volume decreases aerosol drug delivery to the lower respiratory tract.	Set tidal volume greater than the volume of tubing and endotracheal tube between the nebulizer and the patient. For adults it should be set to greater than 500 mL, if appropriate for the patient.
Inspiratory time and duty cycle	Inspiratory time and duty cycle are directly related to bronchodilator delivery during mechanical ventilation. As inspiratory time or duty cycle increases, more aerosol will be inhaled by the patient.	Increase inspiratory time while minimizing the degree of intrinsic positive end expiratory pressure. Duty cycle of 0.3 or greater is recommended.
Flow	Higher inspiratory flow increases turbulence and inertial impaction; thereby reduces bronchodilator delivery.	Use an inspiratory flow of 30–50 L/min, if tolerated .
Bias flow (breath-triggering mechanism)	Increasing the bias flow not only dilutes aerosol but also increases the washout of the aerosol into the expiratory limb between breaths.	Use lower bias flow $\leq$2 L/min with nebulizers. Synchronize the actuations with inspiration when using pMDIs.
Inspiratory waveform	Square waveform delivers less aerosol than decreasing ramp or sinusoidal waveforms.	Choose sinusoidal or decreasing ramp waveforms.

Table 2 Circuit-related factors, their effects and recommendations to optimize bronchodilator delivery in mechanically ventilated adults

Factors	Effects	Recommendations
ETT	Drug delivery decreases with the reduction of the inner diameter of the ETT.	Place the largest diameter ETT that the patient can safely tolerate. Keep ETT clear of secretions.
Heat and humidity	The filter of the HME acts as a barrier to aerosol delivery.	Remove the HME before aerosol drug administration and place it back into the circuit after the treatment.
	Placement of nebulizers between the HME and patient airway may overload the HME and increase work of breathing.	Do not place nebulizers between the HME and patient airway.
	Heated humidifiers reduce aerosol deposition and increase particle size. However, cold dry air is a clear problem.	Do not remove the heated humidifier from the circuit. Increase the dose, as needed for clinical response.
Density of inhaled gas	Heliox creates the persistence of laminar flows in the airways improving aerosol deposition by decreasing particle-impaction losses.	Use heliox 80:20 or 70:30 for optimal delivery of aerosols through the ventilator circuit. Do not dilute less than 50:50 for effect.
	The lower density of Heliox is not as effective in generating aerosol with jet nebs, requiring twofold higher flows, which may alter ventilator parameters.	Use lower flow of oxygen to power jet nebulizers. If you do use heliox, increase the flow rate by twofold.
	Vibrating mesh, ultrasonic nebs and pressurized metered-dose inhalers generate aerosol without being affected by heliox.	Use vibrating mesh, USN or pMDI with spacer when using heliox.
Right angle elbow adapter	Using a right angle elbow adapter decreases aerosol delivery from a pMDI on a humidified ventilator circuit but not on a non-humidified circuit.	Remove the right angle elbow adapter, when using a humidified ventilator circuit.

ETT, endotracheal tube; HME, heat and moisture exchanger; pMDI, pressurized metered-dose inhaler.

Y adapter. pMDIs should always be used with a properly sized adapter (with evidence of performance) during mechanical ventilation, shaken well before administration and the actuation of the pMDI should be synchronized with the beginning of inspiration, with greater than 15 s between actuations.

Recommendations for administration technique

Successful bronchodilator therapy can be best achieved with adequate drug deposition at the intended site of action in the lung and with a focused administration technique (Dhand and Tobin, 1997; Ari *et al*., 2009). Careful attention to bronchodilator administration technique during mechanical ventilation is essential (Duarte, 2004; Dhand, 2008; Guerin *et al*., 2008; Fink, 2009). Figure 2 provides the steps for optimal technique for JN and VM nebulizers as well as pMDI.

Patients should be monitored before, during and after the administration of bronchodilators during mechanical ventilation. Clinicians should also specifically observe heart rate, oxygen saturation, blood pressure, patient-ventilator synchronization and airway resistance during aerosol therapy in patients receiving ventilator support.

Recommendations for future research

In vitro evidence indicates that bronchodilator delivery during mechanical ventilation is affected by many factors. To date, *in vivo* evidence in support of these variables is limited. This is in large part to the flat response curve to beta agonists such as albuterol. However,

Table 3 Device-related factors, their effects and recommendations to optimize bronchodilator delivery in mechanically ventilated adults

Factors	Effects	Recommendations
Position of aerosol device in circuit	The location of the aerosol device in the ventilator circuit significantly affects aerosol drug delivery.	Place the JN closer to the ventilator. Position the pMDI, vibrating mesh and UNs in inspiratory limb 6 in from the Y adapter.
Nebulizer-related factors	*Nebulizer type:*	
	JNs are less efficient than vibrating mesh nebulizers, UNs and pMDIs with spacer.	Choose the VM nebulizer, USN or pMDI with spacer for bronchodilator delivery in mechanically ventilated patients.
	Intermittent and continuous nebulization:	Run the JN intermittently, if ventilator has that option.
	Intermittent nebulization synchronized with inspiration is more efficient for aerosol delivery than is continuous nebulization.	Set the flow rate at 6–8 lpm or as recommended by manufacturer and adjust the ventilator parameters (Vt and pressure), if you run the JN continuously.
	Residual dead volume:	Use the VM nebulizer when possible.
	The greater the dead volume, the less amount of drug is nebulized. JNs do not aerosolize below dead volume of 1–2.5 mL. VM nebulizers have smaller residual volumes than jet or UNs.	In the absence of the VM nebulizer, use a fill volume of 4–5 mL unless the JN is specifically designed for a smaller fill volume.
	Gas flow:	
	The ultrasonic and vibrating nebulizers are not influenced by gas flow as they are electrically powered.	Use the ultrasonic or VM nebulizers for bronchodilator deliver, when possible.
	Operating the JN at a lower flow or pressure than the design will increase particle size and reduce delivery. Gas flow inversely related to nebulization time with the JN.	Set the flow rate at 6–8 lpm or as recommended by manufacturer and adjust the ventilator parameters (Vt and pressure), if you run the JN continuously.
pMDI -related factors	*pMDI actuation:*	
	Synchronized pMDI actuations with inspiration increase bronchodilator delivery.	Synchronize pMDI actuations with inspiration. Actuate at 15 s or greater intervals.
	Spacer:	
	Using a chamber spacer with the pMDI reduces losses in the circuit and increases drug delivery up to sixfold.	Use chamber spacers with the pMDIs for bronchodilator administration to mechanically ventilated patients.
	The efficiency of a bidirectional inline spacer was higher than the efficiency of a unidirectional inline spacer and achieved efficiency marginally less than chamber spacers.	Bidirectional inline adapters are a better option than unidirectional low volume spacers.
	Shaking the canister:	
	The drug in the pMDI formulations are separated when standing. Therefore, not shaking a pMDI canister reduces total and respirable dose up to 35%.	Shake the pMDI before the first actuation of each dose (up to eight puffs) administered.

JN, jet nebulizer; pMDI, pressurized metered-dose inhaler; UN, ultrasonic nebulizer; VM, vibrating mesh.

further research into this area of research is needed in order to examine the impact of optimizing aerosol delivery during mechanical ventilation on physiologic variables and patient outcomes, such as duration of ventilation, intubation and intensive care stays. In addition, optimum agent and dosage with bronchodilator therapy during mechanical ventilation have not been reported. Therefore, studying the effectiveness of varying bronchodilators and dosage schedule is warranted.

In summary, evidence indicates that bronchodilator delivery in mechanically ventilated patients is complex. Tables 1, 2 and 3 summarize the factors that were classified into three categories: ventilator-related factors, circuit-related factors and device-related factors, respectively. They list each factor affecting aerosol drug delivery in mechanically ventilated patients, summarize their effects and make some recommendations for optimizing aerosol drug administration. When these factors are not carefully controlled and the optimum technique for bronchodilator delivery is not utilized, a greater proportion of the aerosol deposits in the ventilator circuit and artificial airways resulting in a decrease in the efficiency of bronchodilator delivery. Therefore, these factors should be carefully controlled during bronchodilator delivery to optimize aerosol delivery for the well-being of patients receiving ventilatory support.

WHAT IS KNOWN ABOUT THIS TOPIC

- It is known that bronchodilator delivery in mechanically ventilated patients is complex because of the factors affecting aerosol delivery in mechanically ventilated patients.

WHAT THIS PAPER ADDS

- This paper provides an up to date review of factors affecting bronchodilator delivery in mechanically ventilated adults.
- This paper explains how to carefully control each factor affecting aerosol deposition to reach therapeutic endpoints of bronchodilator therapy in patients receiving ventilatory support.
- In addition, this paper also provides several recommendations on ventilator settings, circuit- and device-related factors, patient selection and administration technique for bronchodilator delivery in mechanically ventilated patients.

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