Inhaled Bronchodilator Administration During Mechanical Ventilation

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Inhaled bronchodilators are routinely administered to mechanically ventilated patients to relieve dyspnea and reverse bronchoconstriction. A lower percentage of the nominal dose reaches the lower respiratory tract in a mechanically ventilated patient than in a nonintubated subject, but attention to device selection, administration technique, dosing, and patient-ventilator interface can increase lower-respiratory-tract deposition in a mechanically ventilated patient. Assessing the airway response to bronchodilator by measuring airway resistance and intrinsic positive end-expiratory pressure helps guide dosing and timing of drug delivery. Selecting the optimal aerosol-generating device for a mechanically ventilated patient requires consideration of the ease, reliability, efficacy, safety, and cost of administration. With careful attention to administration technique, bronchodilator via metered-dose inhaler or nebulizer can be safe and effective with mechanically ventilated patients. *Key words: aerosol, bronchodilator, mechanical ventilation, β agonist, chronic obstructive pulmonary disease, COPD, asthma, inhalation therapy, noninvasive ventilation.* [Respir Care 2004;49(6):623–634. © 2004 Daedalus Enterprises]

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Introduction

Compared to ambulatory, nonintubated subjects, delivery of inhaled bronchodilators to mechanically ventilated patients differs with respect to the delivered dose, administration technique, and patient-device interface. Bronchodilator administration via inhalation provides therapeutic efficacy similar to systemic administration but with a smaller drug dose[1] and less systemic absorption and thus less adverse systemic effect.[2] In the critical care setting bronchodilators are principally administered via metered-dose inhaler (MDI) or nebulizer. These devices generate aerosol with mass median aerodynamic diameter (MMADs) of 1–5 μm, which is the MMAD range that allows aerosol to reach the lower respiratory tract.[3] MDIs are chiefly used to deliver bronchodilator and corticosteroid aerosols and are considered more efficient than jet nebulizers. Successful aerosol therapy in ventilator-dependent patients requires a precise understanding of the principles that govern aerosol delivery during mechanical ventilation.

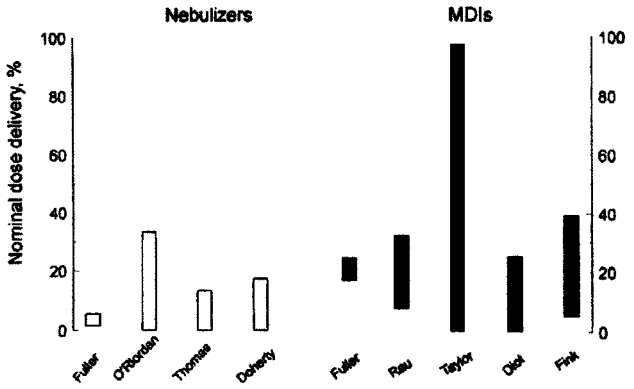

Fig. 1. Deposition values reported in bench models of mechanical ventilation. Note the broad range of values reported (the range is represented by the upper and lower limits of the bars). Depending on the administration technique, between 0 and 97.5% of the nominal dose was deposited in the lower respiratory tract.[6–13] Aerosol delivery was greatest when a metered-dose inhaler (MDI) was actuated into a catheter that directly deposited the aerosol at the distal end of the endotracheal tube. (From Reference 1, with permission).

Lower-Respiratory-Tract Deposition

Compared to a nonintubated subject, a mechanically ventilated patient receives less of a given dose of aerosol in the lower respiratory tract. An initial report examining lower-respiratory-tract delivery of aerosolized radiotracer to intubated, mechanically ventilated patients found that 2.9% of the nominal dose was deposited in the airways, compared with 11.9% in nonintubated subjects.[4] The deposition pattern revealed substantial uptake of radiotracer within the endotracheal tube (ETT), which suggests that the ETT and ventilator circuit are barriers to lower-respiratory-tract deposition. Interestingly, more recent studies have demonstrated that the ETT and ventilator circuit are not as formidable barriers as once believed and that attention to ventilatory variables may significantly influence deposition.[5] Other investigators have reported lower-respiratory-tract deposition to range from 0 to 42% with nebulizers[6–9] and from 0.3 to 97.5% with MDIs (Fig. 1).[10–13] Some of that variability is probably from different aerosol delivery methods and lack of a standard model with which to reliably assess lower-respiratory-tract delivery. With a standardized method and model, the lower-respiratory-tract delivery is similar with nebulizers and MDIs (about 15%).[12,13]

Nebulizer Performance

The most commonly used nebulizers are the jet/pneumatic type, which use compressed gas to create aerosol particles of a size that can reach and deposit in the lower respiratory tract. Ultrasonic nebulizers transform electrical energy into high-frequency vibrations that aerosolize the liquid. Nebulizer performance varies with the gas flow, diluent volume, and operating pressure, and the various nebulizer models differ in performance.[7,9,14] During mechanical ventilation, lower-respiratory-tract deposition is most likely with an MMAD of 1–3 μm; aerosol particles larger than that tend to impact and attach to the ventilator circuit and ETT. Within the limits of a nebulizer's design, the higher the gas pressure and/or flow to the nebulizer, the smaller the MMAD.[14] During mechanical ventilation nebulizers can be operated continuously or intermittently (ie, only during inspiration). Continuous aerosol generation requires a pressurized gas source, whereas intermittent operation requires a separate line to conduct inspiratory airflow from the ventilator to the nebulizer. Intermittent nebulization decreases aerosol loss during exhalation and is thus more efficient than continuous aerosol generation.[15] Importantly, the driving pressure provided by most ventilators to the nebulizer ($<$ 15 psi) is much lower than that provided by compressed air or oxygen sources commonly available in the hospital (50 psi), so the efficiency of some ventilator-powered nebulizers is less than continuous-operation nebulizers powered by a higher-pressure gas but at a similar flow.[16] For mechanical ventilation ultrasonic nebulizers have the advantage that they do not increase the tidal volume (V_T), whereas jet nebulizers can increase V_T.

Metered-Dose Inhaler Performance

Delivering MDI aerosol to a mechanically ventilated patient requires the use of an actuator device that allows the MDI to be discharged into the ventilator circuit. The dose from the MDI is released from the canister through a metering valve and a stem that fits into an actuator boot designed and tested by the manufacturer to work with that specific formulation. The liquid spray leaves the MDI at about 15 m/s, declining by 50% within 0.1 s as the aerosol cloud develops and moves away from the actuator orifice.[17] Actuating the MDI into a chamber-style spacer reduces the velocity of the aerosol jet,[18] thereby allowing time for the propellant to evaporate and for particle size to stabilize and helping to minimize aerosol lost to impaction in the ventilator circuit.

The dose of medication delivered by an MDI is much smaller than that from a nebulizer. The quantity of albuterol delivered by an MDI actuation is only 100 μg, and a careful administration technique is necessary to ensure adequate drug delivery to the lower respiratory tract of a mechanically ventilated patient. Several types of adapters are commercially available to attach an MDI canister to the ventilator circuit or the ETT. The former include chamber adapters, such as cylindrical spacers and reservoir devices, and nonchamber devices. In vitro and in vivo studies have demonstrated that, with MDIs, chamber devices give 4–6-fold better aerosol delivery than elbow adapters (directly attached to the ETT)[10,12,19,20] or inline devices that lack a chamber.[20] Lack of therapeutic effect has been reported with an MDI and elbow adapter attached to the ETT, even with very high doses of albuterol (up to 100 actuations totaling 10.0 mg).[21]

Factors That Influence Lower-Respiratory-Tract Deposition

Aerosol delivery to mechanically ventilated patients is a complex process involving the interaction of several factors. Various elements influence the efficiency of lower-respiratory-tract deposition (Table 1) and attention to these factors affects the efficiency of lower-respiratory-tract delivery.

Table 1. Factors That Influence Lower-Respiratory-Tract-Deposition During Mechanical Ventilation

Physical and chemical properties of the medication
Characteristics of the aerosol-generating device
Position of the aerosol-generating device in the circuit
Ventilator settings
Characteristics of the ventilator circuit and endotracheal tube
Humidity of the inspired air
Airway anatomy and secretions

Endotracheal Tube and Ventilator Circuit

The efficiency of lower airway delivery is reduced by the impaction of aerosol particles inside the ETT and ventilator circuit. With a pediatric ETT (inner diameter of 3–6 mm) it appears that the narrower the ETT diameter, the greater the particle impaction and thus the lower percentage of the dose delivered to the lower respiratory tract.[22,23] Yet the efficiency with which various nebulizers deliver aerosol beyond the ETT did not differ in a study of adult-size ETTs (inner diameter 7–9 mm).[7] Earlier reports overestimated the aerosol-delivery impediment created by the artificial airway, probably because the aerosol generator was placed close to the ETT. Placing the aerosol generating device away from the patient increases pulmonary deposition, though drug losses in the ventilator circuit are higher than those in the ETT. Importantly, the model of aerosol generator and the mechanical ventilation parameters influence aerosol deposition within the ETT more than does the ETT's diameter.[5]

Heating and Humidification

Conditioning the inspired gas involves heating and humidification, which diminishes pulmonary deposition of aerosols, with MDIs and nebulizers, by approximately 40%,[7,9,12,24,25] most likely because of increased particle impaction in the ventilator circuit. Fink et al studied the effect of heating and humidification on MDI albuterol deposition in the ventilator circuit, ETT, and filters in a tracheobronchial model (Fig. 2).[24] They found greater albuterol deposition in the ventilator circuit and ETT with heated, humidified gas and, consequently, less drug delivery to the lung model. Accordingly, some investigators have proposed bypassing the humidifier during aerosol administration.[26,27] The absence of humidification is unlikely to pose a problem during the brief interval required to administer an MDI aerosol. However, some nebulizers require up to 35 min to complete aerosolization,[12] and inhaling dry gas for that long could harm the airway mucosa. In addition, disconnecting the ventilator circuit to bypass the humidifier increases the risk of ventilator-associated pneumonia. Thus it is recommended that MDI or nebulizer delivery of bronchodilators be performed with humidification.

Density of the Inhaled Gas

During mechanical ventilation, high inspiratory flow produces turbulent airflow, which is associated with greater drug particle-impaction losses. Use of a less-dense

gas, such as helium-oxygen mixture (heliox), reduces airflow turbulence and thereby promotes greater drug delivery to the lung.[28–30] In ambulatory subjects with airway obstruction, heliox provides better aerosol lung-retention than air.[29] During mechanical ventilation heliox increases MDI albuterol airway deposition.[28,31] However, the nebulizer should not be powered by heliox, because heliox is less effective at nebulizing the liquid. A practical method to achieve maximum pulmonary aerosol deposition with a nebulizer during mechanical ventilation is to operate the nebulizer with oxygen at a flow of 6–8 L/min and to entrain the aerosol into a ventilator circuit that contains heliox. With that method aerosol delivery to the lower airways of a tracheobronchial model was 50% higher than with oxygen in the ventilator circuit.[31] However, during mechanical ventilation heliox may interfere with the performance of the ventilator, so prior to using heliox the clinician should test and adjust the ventilator to avoid a potentially disastrous patient outcome.[32]

Position of the Aerosol Generator in the Ventilator Circuit

Aerosol delivery is improved by placing the nebulizer 30 cm from the ETT rather than between the Y-piece and the ETT, because the ventilator tubing acts as a spacer for the aerosol to accumulate between breaths.[7,9,15] Furthermore, a modest increase in aerosol delivery is achieved by adding a spacer device in the ventilator circuit between the nebulizer and the ETT.[33]

Ventilation Parameters

The ventilation parameters, including ventilation mode, V_T, flow, and respiratory rate, influence the characteristics of the breath used to deliver aerosol to a mechanically ventilated patient. For optimal aerosol delivery MDI actuation must be precisely at the onset of inspiration. In one study, synchronizing MDI actuation (into a cylindrical spacer) with inspiration resulted in approximately 30% greater aerosol delivery than when actuation occurred during expiration.[12] With an elbow adapter MDI actuation *not* synchronized with the onset of inspiration achieved negligible pulmonary aerosol delivery.[12]

Adequate aerosol delivery can be achieved during assisted ventilation modes, provided the patient's breathing pattern is in synchrony with the ventilator. Up to 23% greater albuterol deposition was observed during

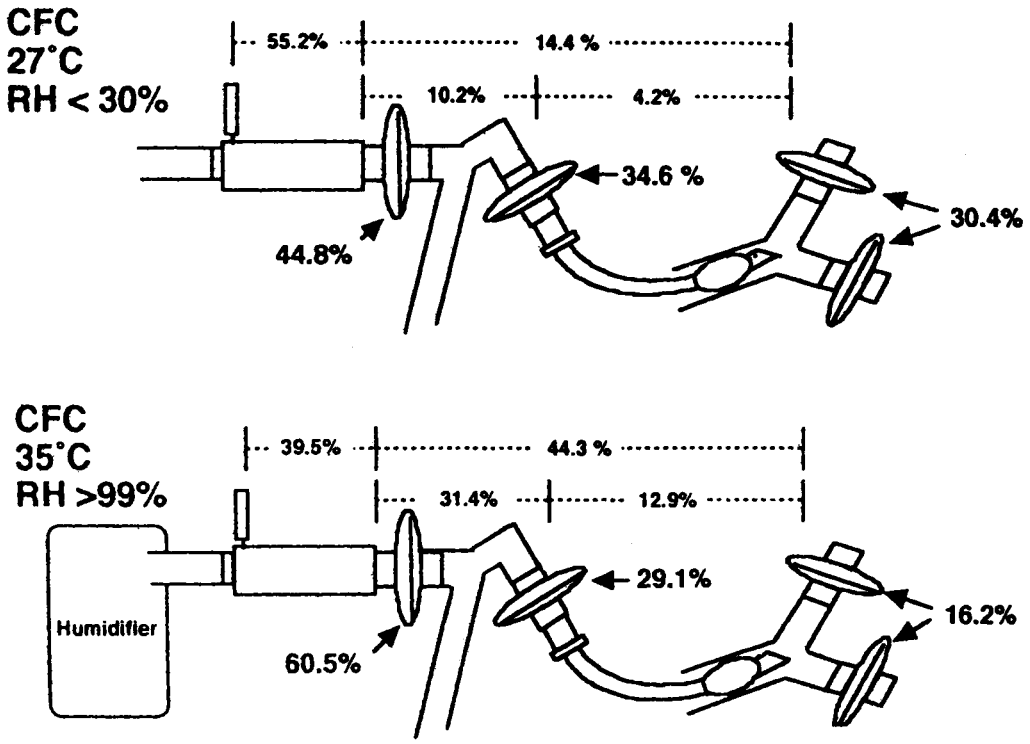

Fig. 2. Albuterol deposition from a metered-dose inhaler, expressed as percent of the nominal dose in the spacer chamber, ventilator circuit, endotracheal tube (ETT), and on filters at the bronchi under dry (top panel) and humidified (bottom panel) conditions. Under dry conditions 55.2% of the albuterol was deposited in the spacer, 10.2% in the ventilator circuit, 4.2% in the ETT, and 30.4% in the bronchi. Under humidified conditions 39.5% of the albuterol was deposited in the spacer, 31.4% in the ventilator circuit, 12.9% in the ETT, and 16.2% in the bronchi. CFC = chlorofluorocarbon. RH = relative humidity. (From Reference 24, with permission).

simulated spontaneous breaths (with continuous positive airway pressure) than during volume-cycled breaths of equivalent V_T.[13] To achieve adequate lower-respiratory-tract delivery the V_T must be larger than the volume of the ventilator tubing and ETT. Thus, with adult patients a V_T of $\geq$ 500 mL is associated with adequate aerosol delivery.[13,34] Increasing the duty cycle (ie, the ratio of inspiratory time to total breathing cycle time) improves lower-respiratory-tract aerosol delivery.[7,13] That relationship applies with nebulizers because a longer inspiratory time allows a larger proportion of the nebulizer-generated aerosol to be inhaled with each breath.[35] Because nebulizers generate aerosol over several minutes, longer inspiratory times have a cumulative effect in augmenting aerosol delivery. In contrast, MDIs produce aerosol over a finite portion of a single inspiration, and the mechanism by which longer inspiratory time increases aerosol delivery is unclear. Finally, several investigators have reported that the efficiency of bronchodilator delivery is not influenced by the inspiratory flow pattern[13,36] or the addition of an end-inspiratory pause.[37]

Clinical Aspects

Patient Selection

A frequently posed question concerns the indications for inhaled bronchodilator therapy. There is a paucity of published information regarding which mechanically ventilated patients should receive inhaled bronchodilator therapy. Bronchodilators reverse bronchoconstriction and decrease airway resistance and consequently relieve dyspnea, so they are indicated for acute asthma or chronic obstructive pulmonary disease (COPD) exacerbation. Bronchodilators should be administered to mechanically ventilated patients who have obstructive airway disease and signs of dynamic hyperinflation, sustained elevation in peak airway pressure, or wheezing episodes. Patients with COPD or asthma who are not having difficulty with mechanical ventilation may receive bronchodilators and should be evaluated for the latter signs.

Following bronchodilator delivery the clinician should observe the patient for improvement, and if there is no objective or clinical improvement, then discontinuing bronchodilators may be appropriate. It is less clear whether mechanically ventilated patients who have a history of smoking or clinically suspected COPD and who are tolerating mechanical ventilation should receive regularly scheduled bronchodilators. Patients with acute respiratory distress syndrome have elevated airway resistance, and several reports have found that nebulized albuterol decreased airway resistance.[38,39] However, increased airway resistance is not a central feature of acute respiratory distress syndrome, so further studies are needed before recommending routine bronchodilator delivery for those patients. Alternatively, a trial of scheduled bronchodilator delivery for 24–48 hours may be considered, but in the absence of improvement in airway measurements, discontinuation of this therapy would be justified. Finally, it is difficult to predict which mechanically ventilated patients will respond to bronchodilators, because neither elevated airway resistance nor expiratory airflow limitation have predictive value.[40]

Bronchodilator Selection

Bronchodilator response has been found following administration of inhaled β-adrenergic[21,38,41–49] and anti-cholinergic agents.[47,50–52] Inhaled isoproterenol,[46,53] isoetharine,[54] metaproterenol,[45] fenoterol[41,47] and albuterol[1,42–44,55,56] have been reported to produce significant bronchodilation when administered to mechanically ventilated patients. There have been no comparison studies of the relative efficacy of β agonists in mechanically ventilated patients, and there is little evidence to support the use of one agent over another.

With mechanically ventilated patients the effect of combining β agonist and anticholinergic has not been extensively evaluated. One report found the combination of fenoterol and ipratropium bromide more effective than ipratropium alone in mechanically ventilated COPD patients.[47]

Administration Technique

Careful attention to the aerosol administration technique during mechanical ventilation is essential for effective therapy. Table 2 shows a technique for administering nebulizer aerosol[26] and Table 3 shows a technique for administering MDI aerosol[1] to mechanically ventilated patients. With mechanically ventilated patients the aerosol administration method often requires a compromise between the optimal operating characteristics of the aerosol generator and the patient's respiratory mechanics. For example, increasing the duty cycle increases pulmonary deposition but may also increase dynamic hyperinflation in patients with airflow limitation from asthma or COPD. The maximum aerosol delivery with a nebulizer during mechanical ventilation (15%) was achieved with a specialty nebulizer (Aero-Tech II) that produces an MMAD < 2 μm (and that requires 35 min for drug administration) with a dry ventilator circuit and a duty cycle of 0.5.[7] Using a commonly available nebulizer with an MMAD of 3.5 μm halves the time for drug administration but also reduces pulmonary deposition to about half of that achieved

Table 2. Using a Nebulizer During Mechanical Ventilation

1. Clear secretions from the endotracheal tube
2. Be sure the tidal volume is > 500 mL
3. If possible, decrease the inspiratory flow to ≤ 60 L/min
4. Place the drug solution in the nebulizer. Total volume in the nebulizer should be 4–6 mL
5. Place the nebulizer in the inspiratory limb, 30 cm from the Y-piece
6. Be sure the gas flow to the nebulizer is ≥ 6 L/min
7. If possible, nebulize the solution only during inspiration
8. Tap the nebulizer intermittently during operation
9. When nebulization ends, disconnect the nebulizer from the ventilator circuit

under optimal conditions (ie, approximately 7.5%). Humidification reduces drug delivery by an additional 40% (deposition down to 4%), and a duty cycle of 0.25–0.33 (which is more commonly employed) is expected to reduce deposition to 2% of the nominal dose (ie, only 50 μg of albuterol delivered to the lung). That amount is similar to the 60 μg of albuterol expected from 4 MDI (with chamber) puffs in a humidified circuit (15% deposition). Although the amount of drug placed in the nebulizer is several times greater than that delivered from an MDI, the devices probably deliver comparable amounts of drug to the lower respiratory tract of a mechanically-ventilated patient. Recent studies have established that using a spacer with an MDI improves the efficacy of bronchodilator therapy in mechanically ventilated patients. The best results are obtained when the MDI actuation is synchronized with the onset of inspiration.[12,43] With careful attention to the administration technique, a bronchodilator response can be expected in most mechanically ventilated asthma or COPD patients.

Assessing Response

The main goal of aerosol therapy is to maximize drug deposition in the lower respiratory tract and minimize adverse drug effects. However, increasing drug deposition in the lower respiratory tract does not necessarily increase therapeutic effect. The response to bronchodilator administration depends on several variables, including patient airway geometry, degree of airway responsiveness, severity of disease, quantity of airway secretions, counter-regulatory effects of airway inflammation, and interactions with other drugs in the patient. Evaluating bronchodilator response requires physical examination, including attention to breathing pattern and auscultation; however; the physical examination findings may not accurately reflect changes in airway caliber. Therefore, measurements of airway pressure, airway resistance, and flow limitation have been proposed to more accurately assess bronchodilator response.

Table 3. Using a Metered-Dose Inhaler During Mechanical Ventilation

1. Clear secretions from the endotracheal tube
2. Be sure the tidal volume is > 500 mL
3. If possible, decrease the inspiratory flow to ≤ 60 L/min
4. Be sure the actuator-spacer device is in the inspiratory limb
5. Shake the MDI and place it into the actuator-spacer device
6. Actuate the MDI at the onset of inspiration
7. Wait 20–30 s before administering the next MDI actuation

MDI = metered-dose inhaler

Most investigators have assessed bronchodilators' clinical efficacy by their effect on inspiratory airway resistance. Airway resistance in mechanically ventilated patients is commonly measured by performing rapid airway occlusions at constant-flow inflation.[57,58] This technique involves performing a breath-hold at end-inspiration by occluding the expiratory port. Graphic displays of the airway pressure profile reveal that airway occlusion immediately decreases airway pressure (P_{peak}) to a lower initial pressure (P_{init}), from which a gradual decline occurs over 3–5 s to a plateau pressure (P_{plat}) (Fig. 3). Similarly, airway occlusion at end-expiration increases airway pressure to a constant value, which is the intrinsic positive end-expiratory pressure (see Fig. 3).[43,59] In a passively ventilated patient and using a square-wave inspiratory flow pattern, the respiratory mechanics are calculated as follows:

$$R_{rsmax} = (P_{peak} - P_{plat})/\text{airflow}$$

$$R_{rsmin} = (P_{peak} - P_{init})/\text{airflow}$$

$$R_{rs} = R_{rsmax} - R_{rsmin}$$

in which R_{rsmax} is the entire resistance of the respiratory system, R_{rsmin} is the "ohmic" resistance (the resistance of the conducting airways, as opposed to the resistance of the entire thorax), and R_{rs} is the additional effective resistance from time-constant inhomogeneities within the lung (pendelluft) and the viscoelastic behavior of the pulmonary tissues. In most mechanically ventilated COPD patients airway resistance and PEEPi decrease following bronchodilator administration.[21,37,42,43,49] Although there are no established threshold values, an R_{rsmax} decrease of > 10% may indicate significant bronchodilator response in mechanically ventilated patients.

Bronchodilator Dosing

Based on the finding that aerosol deposition is markedly lower in mechanically ventilated patients than in nonintubated patients, higher bronchodilator doses were recommended for mechanically ventilated patients.[60]

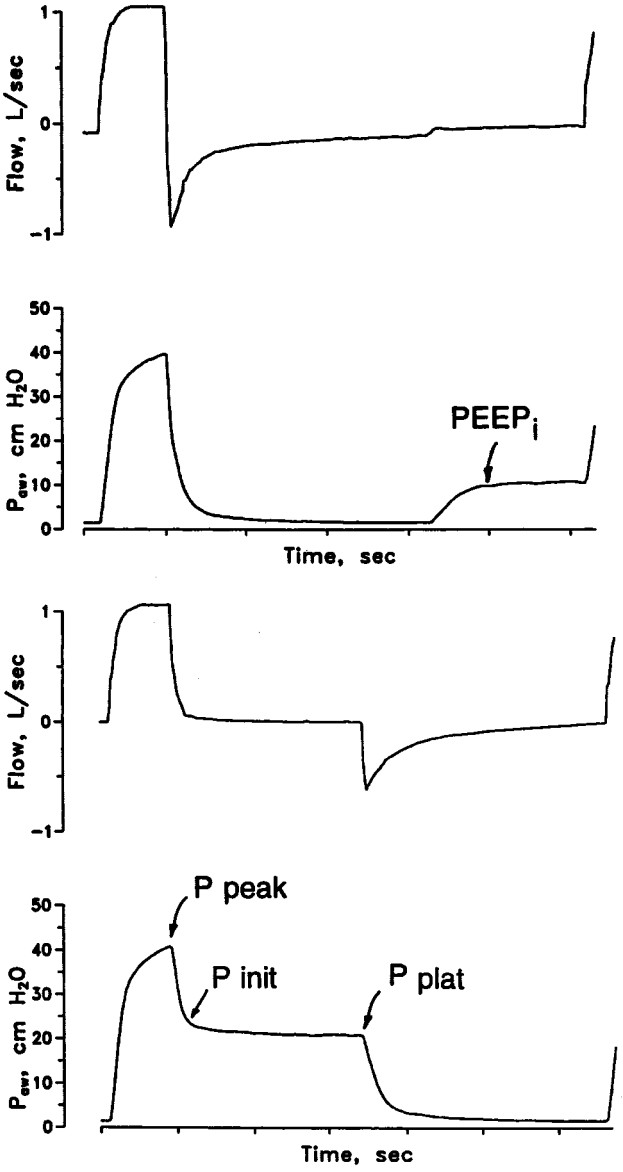

Fig. 3. Airflow and airway pressure (P_{aw}) tracings from a mechanically ventilated patient with chronic obstructive pulmonary disease (COPD). The figure shows the effect of rapid airway occlusion at end-expiration (upper 2 panels) and at end-inspiration (lower 2 panels). End-expiratory occlusion increases airway pressure, and its plateau value determines the intrinsic positive end-expiratory pressure ($PEEP_i$). End-inspiratory occlusion rapidly decreases peak pressure (P_{peak}) to a lower initial pressure (P_{init}), followed by a gradual decline to a plateau (P_{plat}). (From Reference 43, with permission).

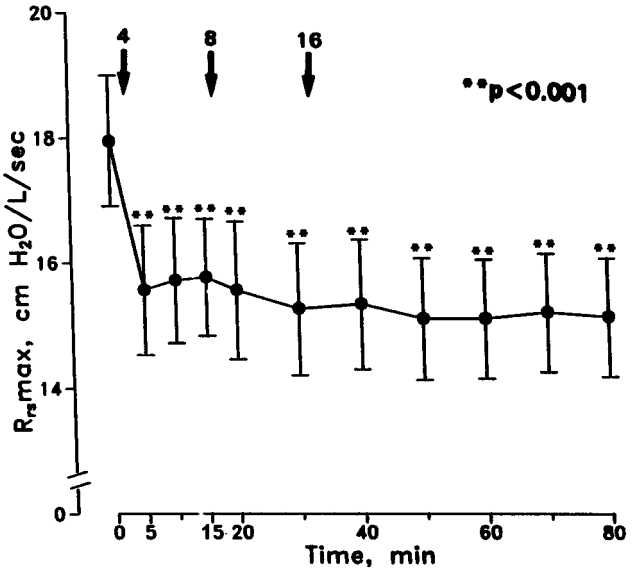

Fig. 4. Effect of albuterol on maximum inspiratory airway resistance of the respiratory system (R_{rsmax}). R_{rsmax} significantly decreased within 5 min of 4 puffs of albuterol. Administration of 8 puffs and 16 puffs (cumulative doses of 12 and 28 puffs, respectively) of albuterol also significantly reduced R_{rsmax} below baseline ($p < 0.001$). The decrease in airway resistance with cumulative doses of 12 and 28 puffs was not significantly greater than with 4 puffs ($p > 0.05$). The error bars represent the standard error of the mean. (From Reference 42, with permission).

However, the precise dosing regimen was not specified, leading some investigators to propose that bronchodilator dosing should be titrated to a physiologic effect.[21] Studies of bronchodilator dose response in mechanically ventilated patients demonstrated significant response with 2.5 mg of albuterol via nebulizer[21,61] (Fig. 4) or 4 MDI puffs (400 μg) (Fig. 5).[42,61] Minimal therapeutic advantage was gained by administering higher doses, whereas the potential for adverse effects increased.[21,42] In patients with severe airway obstruction or if the administration technique is not optimal, higher doses may be required.

The duration of bronchodilator effect was studied with a group of stable, mechanically ventilated COPD patients. The response pattern was similar when optimizing the ventilator settings and the effect of 2.5 mg of nebulized albuterol was similar to that of 4 puffs from an MDI with spacer (Fig. 4).[61] However, further studies are needed to assess the duration of the bronchodilator effect and establish a rational dosing schedule in mechanically ventilated patients. In summary, with a carefully executed administration technique, most stable mechanically ventilated COPD patients achieve near-maximal bronchodilation from 4 MDI puffs or 2.5 mg of nebulized albuterol.

Toxicity

Higher doses of β agonists are associated with higher risk of serious arrhythmia and hypokalemia, but no serious adverse effects have been reported after bronchodilator

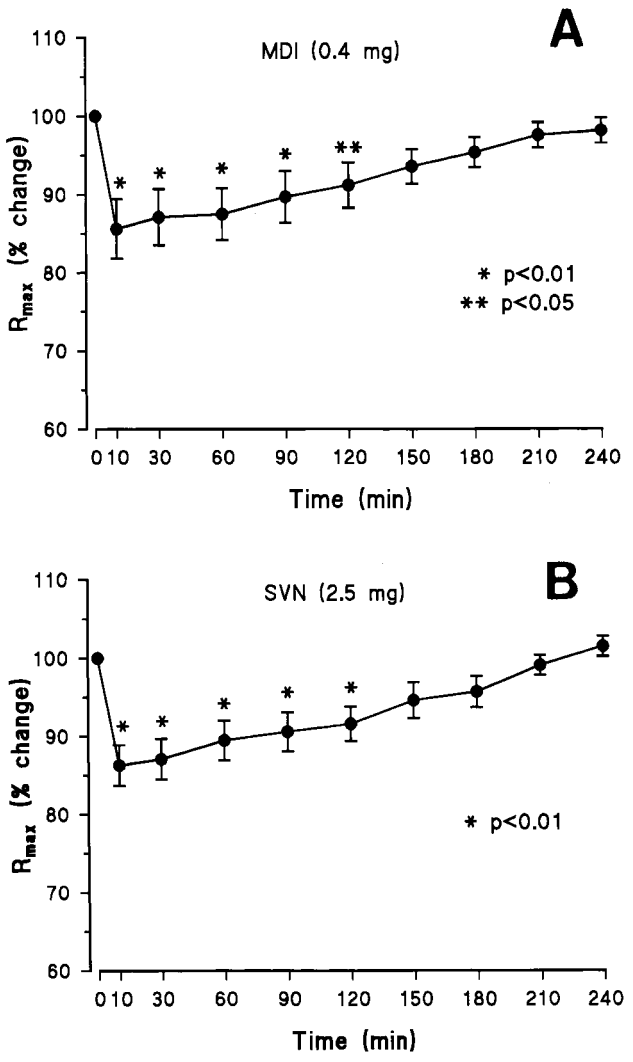

Fig. 5. Effect of albuterol on maximum inspiratory airway resistance (R_{max}). R_{max} significantly decreased (compared to baseline [$p < 0.01$]) within 10 min of albuterol administration. A: R_{max} change (from baseline) after 4 metered-dose inhaler (MDI) puffs of albuterol. B: R_{max} change (from baseline) after 2.5 mg albuterol via small-volume nebulizer (SVN). Significant R_{max} reduction was sustained for 120 min and returned to baseline at 240 min. The response pattern was similar with MDI and nebulizer delivery in a group of stable, mechanically ventilated patients with chronic obstructive pulmonary disease. The error bars represent the standard error of the mean. (From Reference 61).

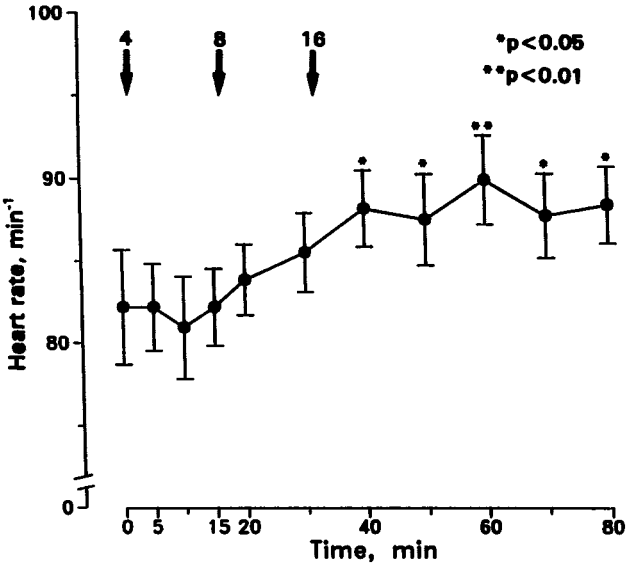

Fig. 6. Effect on heart rate of increasing albuterol dose. Heart rate did not change after 4 puffs or a cumulative dose of 12 puffs ($p > 0.05$). After a cumulative dose of 28 puffs heart rate increased significantly ($p < 0.01$) and was significantly higher than baseline at 80 min ($p < 0.05$). The error bars represent standard error of the mean. (From Reference 42, with permission).

administration to mechanically ventilated patients. Dhand et al reported a significant increase in heart rate following a cumulative dose of 28 MDI puffs of albuterol (Fig. 6).[42] Episodes of supraventricular tachycardia and ventricular ectopy occurred following administration of 3–6 times the normal nebulized dose of albuterol,[21] but no arrhythmias were observed following administration of 4–10 MDI puffs of albuterol.[42,43,61]

Concern regarding the toxicity of chlorofluorocarbon propellants in MDIs is negligible, because chlorofluorocarbons have a very short half-life (< 40 s) in the blood.[62] However, when very high doses are administered from an MDI or when a catheter is attached to the MDI nozzle to deliver aerosol directly to the main bronchus, beyond the ETT tip,[11,63] the chlorofluorocarbon could be cardiotoxic.[64] Also, the catheter aerosol-delivery system can produce localized ulceration in the respiratory tract,[65] an effect attributed to oleic acid, which is a surfactant in some MDI formulations.

Metered-Dose Inhaler Versus Nebulizer

The efficacy of an aerosol-generating device can be evaluated via in vitro measurements, scintigraphy, pharmacokinetics, clinical outcomes, and cost analysis. Each assessment method is required in the development and use of an aerosol device, and a composite evaluation of the assessment methods is required for the clinician. Traditionally, MDIs have been prescribed for out-patient treatment, whereas nebulizers have been more frequently used in in-hospital visits. This has led to the erroneous belief that nebulizers are preferred for bronchodilator delivery in critically ill patients. In fact, several investigators have demonstrated MDI and nebulizer to be equally effective with spontaneously breathing

patients suffering obstructive lung disease.[60] Likewise, MDIs and nebulizers have been reported to deliver a bioequivalent mass of aerosol beyond the ETT in a model of mechanical ventilation.[12] In mechanically ventilated patients lower-respiratory-tract deposition of inhaled bronchodilator via nebulizer is in the range of 1.2 to 3%, whereas with MDI it is approximately 5.6%, as compared to 12–14% in nonintubated, spontaneously-breathing subjects.[4,8,66,67] Still, MDI and nebulizer bronchodilator produce similar therapeutic effects in mechanically ventilated patients.[61]

For mechanically ventilated patients, MDIs are preferred for routine bronchodilator therapy because of several problems associated with nebulizers. The rate of nebulizer aerosol production is highly variable, not only among different brands of nebulizer but among different batches of the same nebulizer model.[68] In addition, the aerosol particle size is highly variable among different nebulizers,[7,14,68] and nebulizer efficiency varies with inspiratory flow, pressure of the driving gas, and fill volume. Also, the efficiency of some nebulizers is drastically decreased when they are operated with gas flow from the ventilator, because that pressure is much lower than from an air compressor unit. Furthermore, a change in ventilator settings leading to a decrease in inspiratory time may lead to diminished functional time of a nebulizer. Therefore, before using a nebulizer with a mechanically ventilated patient, it is imperative to characterize the aerosol-delivery efficiency with the intended ventilator and clinical conditions.

Nebulizers have been associated with bacterial contamination, so they must be scrupulously cleaned and disinfected to minimize the risk that they will aerosolize bacteria[69] and thus increase the risk of nosocomial pneumonia.[70] During continuous nebulizer operation the gas flow driving the nebulizer produces additional airflow in the ventilator circuit, which requires adjusting the V_T and inspiratory flow. The additional gas flow from the nebulizer can create a situation in which the patient is unable to trigger the ventilator during pressure support ventilation, which can cause hypoventilation.[71] In contrast, MDIs are easy to administer, require less personnel time, provide a reliable dose, and do not pose a risk of bacterial contamination. Using a bench model of mechanical ventilation, Hess et al demonstrated more reliable bronchodilator delivery with an MDI-with-spacer than with a nebulizer.[35] When the MDI is used with an inline spacer, the ventilator circuit need not be disconnected, thereby reducing the risk of ventilator-associated pneumonia. In summary, MDIs offer several advantages over nebulizers for routine bronchodilator therapy to mechanically ventilated patients.

Bronchodilator therapy accounts for a substantial percentage of the cost of care of mechanically ventilated COPD patients.[72] It would be useful to conduct a cost-effectiveness analysis of MDI versus nebulizer delivery of bronchodilators and compare their outcomes and costs. However, equipment, medication, and labor costs differ among hospitals, making it difficult to conclusively determine whether MDI or nebulizer is more cost-effective.[73] Conversion from nebulizer to MDI delivery has been reported to lower costs and save time.[74] Bowton et al found that substituting MDIs for nebulizers in a 700-bed hospital decreased potential patient costs of aerosol therapy by $300,000 a year.[75]

Bronchodilators Via Noninvasive Ventilation

MDIs and nebulizers has been used to deliver bronchodilator during noninvasive ventilation.[76,77] One study randomized patients with acute bronchospasm to receive either nebulized albuterol alone or nebulized albuterol delivered through a portable bi-level ventilator circuit and nasal mask. The patients who received albuterol via the ventilator had greater improvement in peak flow.[78] Recently, Chatmongkolchart et al used a bench model to examine nebulized albuterol delivery under varying inspiratory and expiratory pressure settings and found marked variability in albuterol delivery. The greatest delivery occurred when the nebulizer was placed between the leak port and the patient connection while applying 20 cm H_2O inspiratory pressure and 5 cm H_2O expiratory pressure.[79] Nava et al reported a bronchodilator response after 4 puffs of albuterol from an MDI with spacer to 18 stable COPD patients undergoing noninvasive ventilation via face mask.[80] Bronchodilator delivery with noninvasive ventilation is feasible, and attention to the technique and placement of the aerosol-generating device are important. Further airway deposition and clinical outcome studies will be necessary before applying noninvasive-ventilation aerosol delivery with patients in acute respiratory failure.

Summary

Inhaled bronchodilators are commonly administered to mechanically ventilated patients and are a considerable component of the cost of care. Careful attention to the factors that influence lower-respiratory-tract deposition in mechanically ventilated patients is required to optimize drug delivery and, thus, patient response. When administration is carefully executed, bronchodilator administration via MDI or nebulizer is safe and effective for mechanically ventilated patients.

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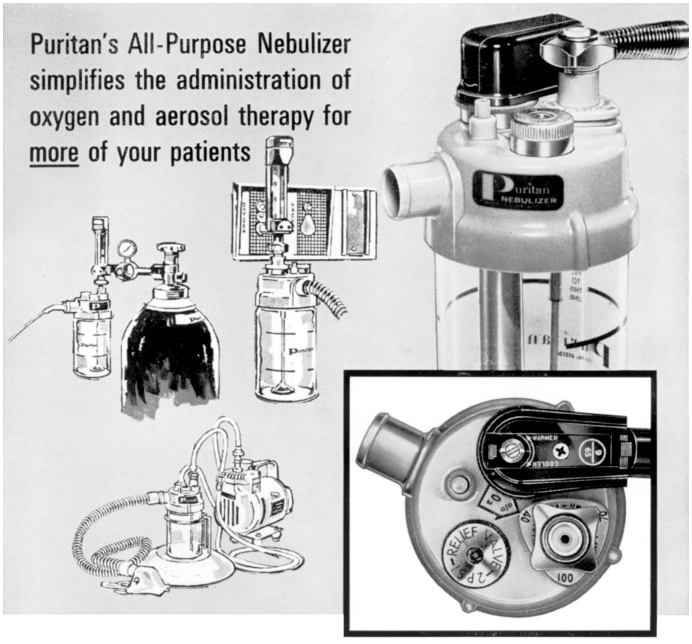

"Puritan's All-Purpose Nebulizer...". Back pages advertisement by Puritan Compressed Gas Corporation in *Inhalation Therapy*, Journal of the American Association of Inhalation Therapists, Vol 11, No. 5, October 1966.