Basic Techniques for Aerosol Delivery During Mechanical Ventilation

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Among the devices employed for aerosol generation (metered-dose inhalers, nebulizers, and dry powder inhalers) only metered-dose inhalers and nebulizers are routinely employed for aerosol delivery to mechanically ventilated patients. The ventilator circuit and artificial airway were previously thought to be major barriers to effective aerosol delivery to mechanically ventilated patients. In the past decade in vitro and in vivo investigations have contributed to a better understanding of the complex array of factors that influence inhaled drug delivery in mechanically-ventilated patients. Several investigators have shown that with careful attention to the administration technique aerosol delivery efficiency in mechanically-ventilated patients is comparable to that in ambulatory patients. The ability to efficiently deliver aerosols should lead to wider clinical application of inhaled therapies in patients receiving mechanical ventilation. *Key words: aerosol, mechanical ventilation, noninvasive ventilation.* [Respir Care 2004;49(6):611–622. © 2004 Daedalus Enterprises]

Introduction

The practice of delivering aerosolized medications for the treatment of asthma is believed to have originated in the Indian subcontinent almost 4,000 years ago.[1] However, a better understanding of the factors that influence aerosol delivery in ambulatory patients occurred only during the latter half of the 20th century. The principles involved in aerosol delivery to mechanically ventilated patients were identified over the past 15 years. The scientific basis for administering inhaled therapies to mechanically ventilated patients is now firmly established.

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Table 1. Advantages of Inhaled Therapy

Direct delivery of drug to site of action
Rapid onset of action
Lower dose (than systemic administration) to produce desired effects
Minimizes systemic adverse effects

The indications for inhaled therapies are rapidly expanding. Aerosolized drugs and agents hold promise for treating pulmonary as well as systemic disorders. The advantages of inhalation therapy for treating respiratory disorders are well known (Table 1).[2] Because the drug or agent is delivered directly to its site of action, there is a rapid onset of drug effect. Moreover, a much smaller quantity of aerosolized drug is needed to produce an effect comparable to that obtained with larger amounts of the same drug administered systemically. Therefore, by specifically targeting the drug to the respiratory tract, systemic absorption of the drug can be limited and adverse effects minimized. In mechanically ventilated patients therapeutic agents currently given via inhalation include bronchodilators, corticosteroids, antibiotics, prostaglandins, and surfactant.[3] Aerosols of several other agents, including immunomodulators, hormones, mucolytics, and genetic therapies, are currently being tested.

Many barriers were previously thought to preclude effective aerosol therapy in the mechanically ventilated patient. Current aerosol-generating devices (metered-dose inhalers [MDIs], nebulizers, and dry powder inhalers) all produce aerosols in which the particles have a mass median aerodynamic diameter between 1 and 5 μm.[4] Of those devices only MDIs and nebulizers can be adapted for use during mechanical ventilation. In the past none of the commercially available devices were specifically designed to generate aerosols in ventilator circuits. Although MDIs and nebulizers were adapted for use in ventilator circuits, the poor efficiency of aerosol delivery to the lung[5,6] was a substantial drawback. Aerosol delivery efficiency is impaired by drug deposition in the ventilator circuit and artificial airway.[7,8] Until recently the techniques needed to effectively employ MDIs and nebulizers were inadequately understood and ventilators were not designed to optimize inhaled drug therapy. With improvements in technology and better understanding of the principles of aerosol delivery many of the obstacles to efficient aerosol delivery during mechanical ventilation have been overcome.[9] In the present report I review the investigations that established the scientific basis for aerosol delivery during mechanical ventilation and describe the current practice of aerosol administration to the mechanically ventilated patient.

Factors That Influence Aerosol Delivery During Mechanical Ventilation

Successful inhalation therapy depends on adequate drug deposition at the intended site of action in the lung. Optimizing drug delivery to the lung requires consideration of a multitude of factors that influence aerosol delivery in the mechanically ventilated patient.[3,10]

To determine lung deposition in mechanically ventilated patients investigators employed gamma scintigraphy after administration of radiolabeled aerosols.[5,6] They found that the efficiency of aerosol deposition was significantly lower in mechanically ventilated patients than in ambulatory patients.[5,6] Thus, in the early 1990s the consensus was that the ventilator tubing and endotracheal tube (ETT) were formidable barriers to effective drug delivery in mechanically ventilated patients. The low efficiency of drug delivery meant that much larger drug doses were needed for ventilated patients than for ambulatory patients.[11] Recently optimal aerosol delivery techniques for ventilated patients have been defined[3,10] such that the efficiency of drug delivery to ventilated patients now matches[12] and may soon surpass that in ambulatory patients.

Methods to Assess Aerosol Delivery During Mechanical Ventilation

A complex array of factors influence aerosol delivery during mechanical ventilation (Fig. 1),[13] including variables related to the aerosol-generating device, the ventilator, the ventilator circuit, the inhaled drug or agent, and the patient. Both in vitro and in vivo methods have been employed to clarify the complex issues surrounding inhaled drug delivery to the mechanically ventilated patient.[3,10] It is important to clarify that in vitro methods measure drug delivery only to the lower respiratory tract, whereas in vivo methods measure drug deposition in the lung. That distinction is important, because not all of the aerosol that reaches the lower respiratory tract deposits in the lung; a portion is exhaled. The amount of exhaled drug and the site of drug deposition cannot be assessed by most in vitro methods. That drawback of in vitro assessment methods can be partially overcome by using a "mass balance" technique that matches ventilator circuits and ventilator parameters to determine the correlation between the results of in vitro and in vivo tests.[12,14]

In Vitro Studies

Carefully performed in vitro tests that simulate the conditions of clinical use have played an important role in determining the optimal techniques for administering aerosols to mechanically ventilated patients.[7,12,14–24] Table 2 describes bench-model studies of aerosol delivery during

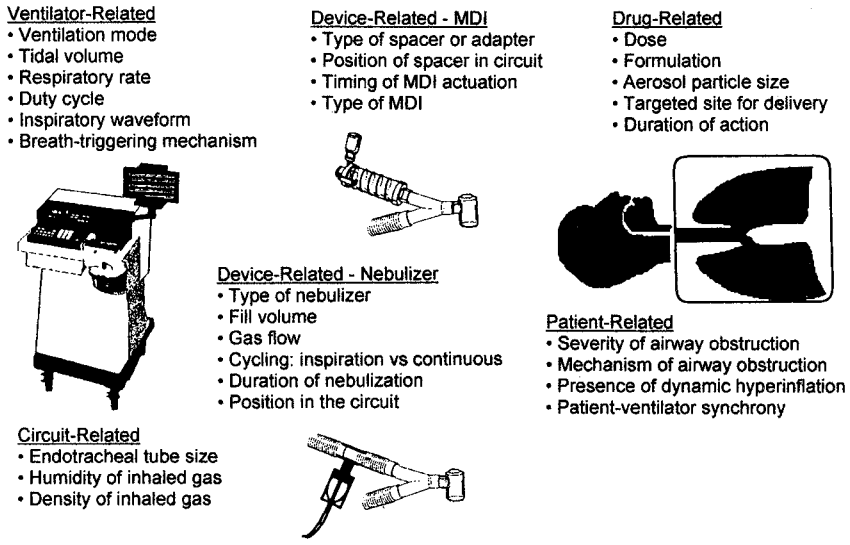

Fig. 1. Factors that influence aerosol delivery in mechanically ventilated patients. MDI = metered-dose inhaler. (Adapted from Reference 13).

Table 2. Determination of Lower-Respiratory-Tract Deposition of MDI Aerosol Using In Vitro Models

Type of Model	Type of Adapter	Breath Type	Measurement	Results
ETT (6.0, 7.5, and 9.0 mm) in trachea[15]	Swivel adapter	Continuous flow or MDI actuation then flow	Filter weight	Greater efficiency with larger ETT and actuation into continuous flow
ETT and laser spectrometer[16]	Three different adapters inline or cylindrical spacer	V_T 800 mL, flow 60 L/min	Particle volume 1–5 μm	Adapters produced lower volume of particles than standard actuator
Ventilator circuit, 8-mm ETT[25]	Swivel adapter at ETT or cylindrical spacer	V_T 800 mL, flow 48 L/min	Albuterol assay	Greater deposition with cylindrical spacer
ETT and laser spectrometer[17]	Nine different MDI spacers or adapters	NA	Particle volume 0.7–5.0 μm	Chamber spacers delivered greater volume than other adapters
Ventilator circuit[18]	MDI with large-chamber or small-chamber spacer	V_T 700 mL, flow 50 L/min	Radioactivity	Similar delivery with the devices
Plastic syringe and simulated carina[23]	MDI with catheter	NA	Albuterol assay	> 90% of dose delivered beyond ETT
ETT (6 mm) and swivel adapter[26]	Catheters placed in ETT (13 or 22 cm long)	Flow 30 L/min	Albuterol assay	Longer catheters delivered greater dose than shorter catheters
Model of trachea and main bronchi[7]	Cylindrical spacer, 8-mm ETT	Flow 40 L/min	Albuterol assay	Decreased deposition with humidification and CMV breaths

MDI = metered-dose inhaler
ETT = endotracheal tube
V_T = tidal volume
NA = informaton not available
CMV = controlled mechanical ventilation

mechanical ventilation.[7,15–18,23,25,26] Initially, investigators collected the aerosol output on filters placed at the end of the ETT and measured drug deposition by the change in the filter's weight,[15] but that technique had obvious drawbacks. Other investigators used laser particle analysis of the aerosol flume,[16,17] but that technique did not measure the amount of drug delivered. Measurements of radiolabeled drug delivery can be influenced by the type of radioactive label employed.[12,14,18,19] Recently, most investigators have directly measured the amount of drug deposited

on the filter. Direct drug assays are a simple, safe, and inexpensive method for measuring aerosol deposition.[7,20–22]

Most bench models have collected the aerosol at the distal end of the ETT.[15–18] Other investigators used a plastic syringe barrel with a simulated carina to quantitate aerosol deposition in the lower trachea.[23] Fink et al employed a plastic model that was constructed to match the dimensions of an adult human trachea and its bifurcation into 2 major airways. They placed the ETT within the trachea, inflated the cuff, and collected the aerosol on filters placed at the ends of the simulated major bronchi.[7,21] That model reproducibly simulates aerosol delivery to the major airways in mechanically ventilated patients.

The factors that significantly influence aerosol delivery in mechanically ventilated patients, as elucidated by in vitro studies, are discussed below.

Aerosol-Generating Devices. Both MDIs and nebulizers are employed to deliver inhaled therapies to mechanically ventilated patients. The majority of drug particles in MDI and nebulizer aerosols are in the range of 1–5 μm. During mechanical ventilation larger aerosol particles are trapped in the ventilator circuit and ETT. With an MDI with spacer, the aerosol emerging from the distal end of the ETT has a mass median aerodynamic diameter of approximately 2 μm.[24] Likewise, nebulizers that produce aerosols with mass median aerodynamic diameter of < 2 μm are more efficient for aerosol delivery during mechanical ventilation than are nebulizers that produce aerosols with larger particles.[14,15,27] However, nebulizers that produce a smaller particle size may require considerably more time to deliver a standard medication dose.[12,24] Approximately 5% of the nominal dose of albuterol emitted from an MDI is exhaled by a mechanically ventilated patient,[21] whereas $< 1\%$ is exhaled by an ambulatory patient.[27] The mean fraction of nebulizer aerosol (7%) exhaled by mechanically ventilated patients is similar to that of MDI aerosol, but there is considerable variability (coefficient of variation 74%) between patients.[14] Whereas MDIs are chiefly used to deliver β adrenergic and anticholinergic bronchodilators or corticosteroids,[3] nebulizers have been used to deliver antibiotics, mucolytics, prostaglandins, and surfactant, in addition to bronchodilators and corticosteroids.[3] The frequency with which MDIs and nebulizers are used in ventilator circuits has changed over the past few years. Traditionally, nebulizers were employed for inhalation therapy during mechanical ventilation, but more and more centers have switched to MDIs for routine bronchodilator therapy. One survey found that 57% of reporting centers use MDIs for bronchodilator therapy in neonates, and the proportion of MDI use had steadily increased since 1988.[28] Although no data are available, the use of MDIs in adult mechanical ventilation is probably higher than in neonatal ventilation.

In bench models of mechanical ventilation the reported efficiency of drug delivery with MDIs has ranged from 0.3 to 97.5%[7,18,21,24–29] and from 0 to 42% with nebulizers.[18,19,24,30–32] These differences in drug delivery underscore the need for optimizing administration techniques with each device.

Configuration of Metered-Dose Inhalers. The MDI canister contains a pressurized mixture of propellants, surfactants, preservatives, flavoring agents, and active drug (the latter composing about 1% of the total contents).[33] The mixture is released from the canister through a metering valve and stem that fits into an actuator boot designed and extensively tested by the manufacturer to work with that specific formulation.[33] Commercially available MDIs are designed for use with ambulatory patients; for an MDI to be employed in a ventilator circuit, the canister must be removed from the actuator supplied by the manufacturer and connected to the ventilator circuit with a different adapter. Several types of commercially available adapters are used to connect the MDI canister to the ventilator circuit (Fig. 2).[20] When an MDI canister is uncoupled from its original actuator and employed with a different actuator (the various circuit adapters), it becomes part of a different device that has different aerosol characteristics and performance. For example, using the canister of a chlorofluorocarbon-propellant MDI in the actuator of a hydrofluoroalkane-propellant MDI (or vice versa) changes the aerosol properties and drug delivery.[21] Likewise the type of MDI propellant formulation[22] and the drug formulation can also influence drug delivery.[20]

Adapters that are used to connect MDIs to ventilator circuits include elbow adapters, inline devices (which may be unidirectional or bidirectional), and chamber or reservoir adapters (see Fig. 2). An elbow adapter connects to the ETT, whereas the inline and chamber adapters are placed in the inspiratory limb of the ventilator circuit. With a chamber spacer the MDI aerosol has an opportunity to slow, and propellant evaporation in the expanding flume decreases the size of the aerosol particles. Both of those phenomena reduce aerosol drug losses caused by particle-impaction on the walls of the ventilator circuit and ETT. In contrast, when an MDI is employed with an adapter connected directly to the ETT, considerable aerosol deposition occurs within the ETT, which may result in negligible therapeutic effects, even after administration of up to 100 MDI doses.[11] Several investigators have shown that employing a chamber spacer with an MDI in a ventilator circuit results in 4–6-fold greater aerosol drug delivery than either an elbow adapter or a unidirectional inline spacer.[16,24,25,34] A bidirectional inline spacer increases the volume of air into which the aerosol is actuated and cor-

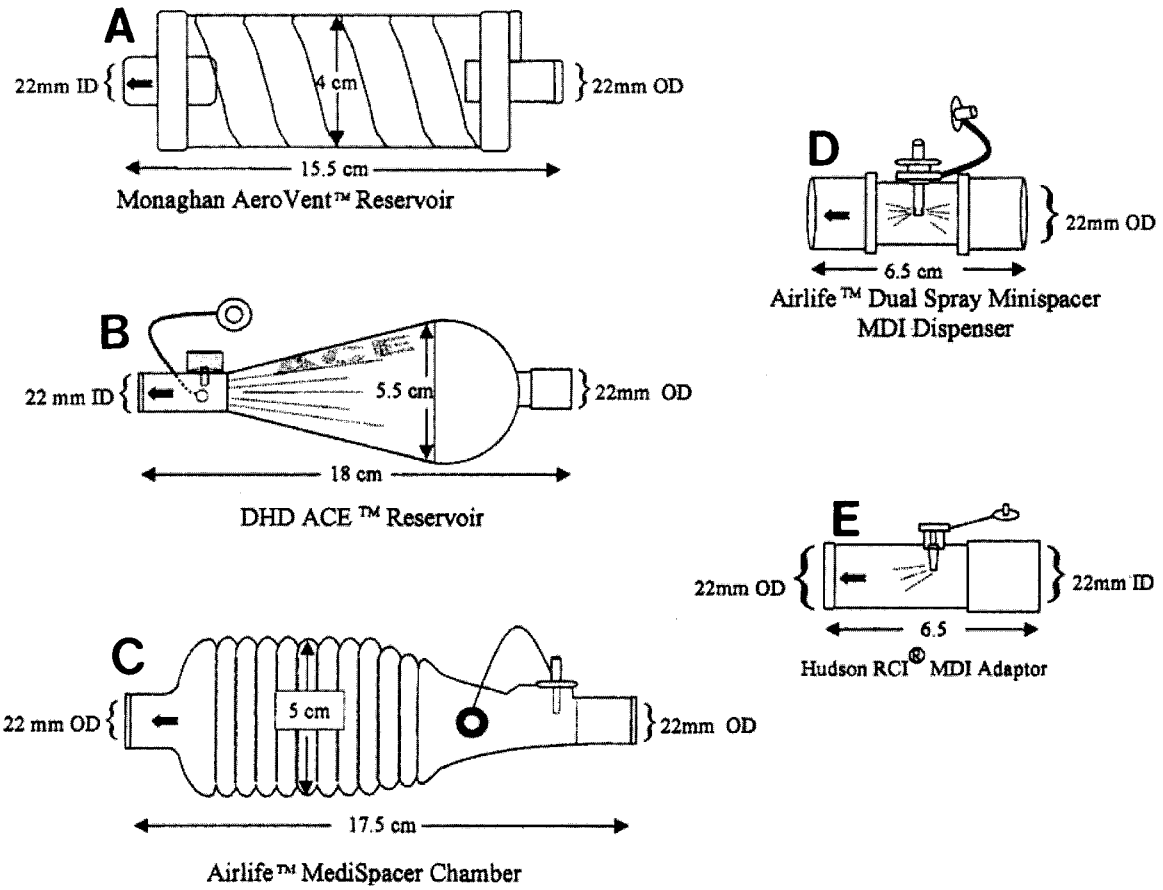

Fig. 2. Commercially available spacers and adapters that are used to connect a metered-dose inhaler canister to a ventilator circuit. A: Collapsible spacer chamber. B: Aerosol cloud enhancer (ACE), wherein the aerosol flume is directed away from the patient. C: Noncollapsible spacer chamber. D: Bidirectional inline adapter. E: Inline adapter. (From Reference 20).

respondingly produces a 1.5–2.5-fold increase in aerosol delivery, compared with a unidirectional inline spacer.[20] The efficiency of aerosol drug delivery with an MDI and bidirectional inline spacer was reported to be comparable with that achieved with chamber spacers.[20] An MDI with chamber spacer connected to the circuit at approximately 15 cm from the ETT provides efficient aerosol delivery to mechanically ventilated patients and elicits significant bronchodilator response.[35]

Configuration of Nebulizers. Both jet and ultrasonic nebulizers are employed for delivering aerosols to mechanically ventilated patients. Nebulizers are connected in the inspiratory limb of the ventilator circuit or at the patient Y-piece. Placing the jet nebulizer at a distance from the ETT offers better efficiency than placing it between the patient Y-piece and the ETT,[19,30,36] because the ventilator circuit serves as a spacer for aerosol to accumulate between inspirations. Adding a reservoir between the nebulizer and ETT also modestly increases the efficiency of drug delivery.[32] One preliminary investigation, which is as yet reported only in abstract form, found that placing a jet nebulizer proximal to the humidifier (ie, between the ventilator and the humidifier) significantly improved the efficiency of drug delivery in a heated, humidified ventilator circuit.[37] Further research is needed to determine the mechanism of that effect and whether that increase in drug delivery substantially impacts aerosol therapy to mechanically ventilated patients.

The efficiency of aerosol generation differs markedly among different nebulizer brands.[19,38] Factors that influence nebulizer efficiency are the diluent volume, operating pressure and flow, and the duration of treatment.[38,39] Within the limits of a particular nebulizer design, the higher the gas pressure and/or flow to the nebulizer, the smaller the particle size generated.[38,39]

The position of an ultrasonic nebulizer in the ventilator circuit also influences its efficiency in delivering drugs to the lower respiratory tract. In a dry circuit drug delivery is better when the ultrasonic nebulizer is placed between the patient Y-piece and ETT than when it is placed close to the ventilator.[37] As with jet nebulizers, drug delivery from an ultrasonic nebulizer is significantly reduced by humidity in the ventilator circuit.[37] The particle size distribution of

the aerosols produced by ultrasonic nebulizers in ventilator circuits has not been well characterized.

Recently, a new generation of nebulizers became available for clinical use. These devices use a vibrating plate or mesh to create aerosol.[40] The Aeroneb Pro (Aerogen, Mountain View, California) is specifically designed for use in a ventilator circuit. It has a higher aerosol delivery efficiency than conventional jet nebulizers[41] and, in contrast to conventional ultrasonic nebulizers, the Aeroneb Pro does not increase the temperature of the solution during nebulization.[42]

Synchronizing MDI Aerosol Generation With Inspiratory Airflow. The actuation of an MDI must be precisely synchronized with the onset of inspiratory airflow from the ventilator. Diot et al found that actuating the MDI (into a chamber spacer) 1–1.5 s prior to the ventilator breath decreased the efficiency of aerosol delivery by 35%.[24] When an MDI was actuated with the adapter connected to the ETT and there was a similar delay in the inspiratory airflow after actuation, negligible drug was delivered.[24] Precise coordination of MDI actuation with the onset of inspiratory airflow from the ventilator ("go with the flow") is important for maximizing MDI drug delivery.[43]

Synchronizing Nebulizer Aerosol Generation With Inspiratory Airflow. There are significant differences in the output efficiency of different nebulizer brands.[19,38] In a ventilator circuit a nebulizer can be operated continuously or intermittently by airflow from the ventilator. Continuous aerosol generation requires a pressurized gas source (from a wall outlet, pressurized tank, or air compressor), whereas intermittent operation requires a separate line to conduct inspiratory airflow from the ventilator to the nebulizer. Intermittent nebulizer operation is more efficient for aerosol delivery than is continuous aerosol generation, because it minimizes aerosol waste during exhalation.[12,36] The driving pressure provided by a ventilator ($<$ 15 psi) is less than that provided by a pressurized gas source ($\geq$ 50 psi). The efficiency of some nebulizers is lower with lower-pressure gas at a similar flow rate.[44] Aerosol generated by a nebulizer operated at the lower pressure will not maximize drug deposition in the lung, because the majority of drug particles will be larger than 5 μm. For intermittent nebulizer operation the specific ventilator and nebulizer brand should be tested to determine the characteristics of the aerosol generated and the efficiency of drug delivery.[12]

Ventilator-Related Factors. The characteristics of the ventilator breath significantly influence aerosol drug delivery. A tidal volume of $\geq$ 500 mL (in an adult) ensures that the dead space is cleared of aerosol, which improves drug delivery to the lower respiratory tract.[7] A longer inspiratory time and slower inspiratory flow improve aerosol delivery in ambulatory[45] and ventilated patients.[7] Drug delivery is linearly correlated with a longer duty cycle (ratio of inspiratory time to total breathing cycle time) with both MDIs and nebulizers,[7,21] although the mechanisms by which that occurs may differ between the 2 devices. With duty cycles of 0.25 and 0.5, MDI drug delivery was significantly better with a slower inspiratory flow (40 L/min) than with a faster inspiratory flow (80 L/min) (Fig. 3).[21] Moreover, drug delivery is better when the MDI is synchronized with a simulated spontaneous breath than with a controlled-mechanical-ventilation breath of similar tidal volume. During spontaneous breaths the amount of drug delivered increased with higher tidal volumes—an effect that was not observed with other mechanical ventilation modes.[7]

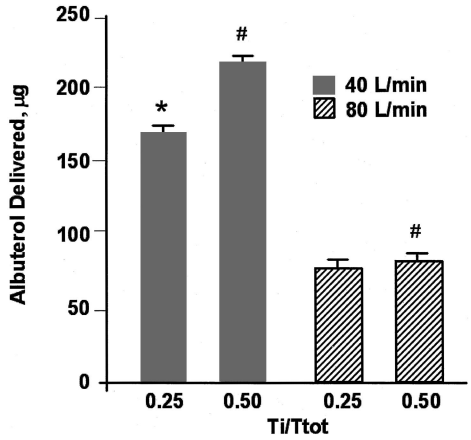

Fig. 3. Comparison of aerosol delivery at different inspiratory airflows and duty cycles (ratio of inspiratory time to total breathing cycle time [T_I/T_{tot}]) in a bench model of mechanical ventilation. The ventilator delivered a tidal volume of 1,000 mL with a constant inspiratory flow of either 40 or 80 L/min and a T_I/T_{tot} of either 0.25 or 0.50 at each inspiratory flow setting. For each T_I/T_{tot} value the slower inspiratory airflow (40 L/min) delivered almost twice as much drug as the faster inspiratory airflow (80 L/min) (* For flow 40 vs 80 L/min $p < 0.01$. # For T_I/T_{tot} 0.25 vs 0.50 $p < 0.01$). (Data from Reference 21).

Recently, Hess et al examined the influence of the inspiratory flow pattern (ie, the inspiratory waveform) on drug delivery.[46] The inspiratory waveform during pressure-controlled ventilation differs from that during volume-controlled ventilation. Moreover, the lung mechanics affect the inspiratory flow pattern and the duration of inspiratory flow during pressure-controlled ventilation. The aerosol-delivery efficiency of the jet nebulizer was influenced by the inspiratory time, inspiratory flow pattern, and lung mechanics[46] and was significantly lower during pressure-controlled ventilation than during volume-controlled ventilation ($p = 0.03$). In contrast, the efficiency of drug delivery from an MDI was not influenced by any of the

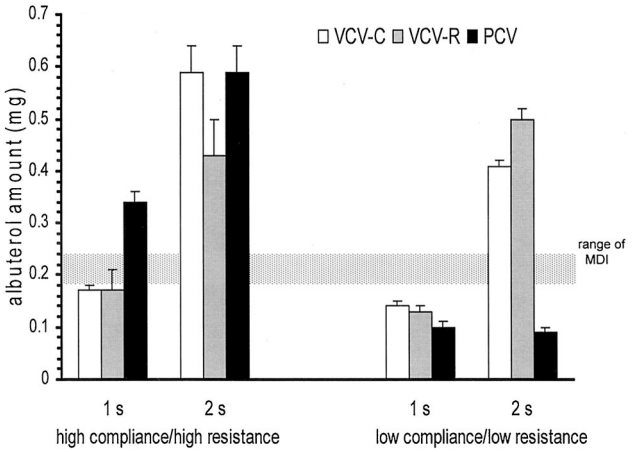

Fig. 4. Comparison of aerosol delivery from a metered-dose inhaler (MDI) and from a jet nebulizer in bench models of pressure-controlled and volume-controlled ventilation. The lung mechanics were varied by selecting 2 settings of resistance and compliance to represent high and low time constants. For each condition the amount of aerosol delivered during inspiratory times of 1 s or 2 s were measured. The nebulizer efficiency was influenced by inspiratory time, pattern of inspiratory flow, and lung mechanics. In contrast, the efficiency with a metered-dose inhaler (MDI, stippled area) remained fairly constant under the various conditions simulated in the bench model. VCV-C = volume-controlled ventilation with a constant inspiratory flow. VCV-R = volume-controlled ventilation with a descending ramp flow pattern. PCV = pressure-controlled ventilation. (From Reference 46, with permission).

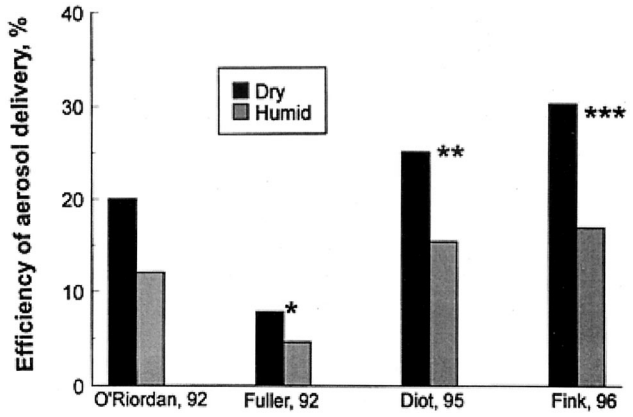

Fig. 5. Effect of humidity on aerosol delivery. The efficiency of aerosol delivery to the lower respiratory tract is shown for bench models of mechanical ventilation with dry and humidified circuits. Humidification reduced aerosol delivery by approximately 40%. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$. (From Reference 10, with permission).

factors mentioned above and remained remarkably consistent under the various study conditions (Fig. 4).[46] The breath-triggering mechanism does not significantly influence drug delivery from an MDI, but use of a flow trigger with a nebulizer could dilute the aerosol and increase the washout of the aerosol into the expiratory limb between breaths.[7] During flow-by additional gas flow from the nebulizer could interfere with the ventilator's ability to sense the onset of the patient's inspiratory effort.

The type of ventilator used also influences the efficiency of drug delivery with a nebulizer.[12,44] Matching the ventilator with the nebulizer is required to better control the delivery of inhaled drugs in mechanically ventilated patients.

Circuit-Related Factors: Heat and Humidity. The gas in the ventilator circuit is heated and humidified to prevent drying of the airway mucosa, but humidification increases loss of aerosol in the ventilator circuit[20] and several investigators have found that both MDI and nebulizer delivery to the lower respiratory tract is reduced as much as 40% by humidification (Fig. 5).[12,18,19,21,24,31] Circuit humidity increases the size of aerosol particles from a nebulizer.[47] With an MDI aerosol humidity probably interferes with propellant evaporation, which keeps the particles larger and thus increases particle-impaction losses.[48–50]

Although circuit humidity reduces drug delivery, bypassing the humidifier is not recommended for routine inhalation therapy in mechanically ventilated patients. Bypassing the humidifier would require disconnecting the circuit, waiting several minutes for the circuit to dry, and reconnecting the circuit. An MDI treatment can be completed in a few minutes, whereas with some nebulizers treatment may require 45–60 min. Inhaling dry gas for extended periods could be detrimental to the tracheal mucosa. Moreover, with careful attention to the administration technique the impact of humidity on drug delivery can be overcome by delivering a somewhat higher dose.[35]

Circuit-Related Factors: Gas Density. The density of the inhaled gas influences lung deposition.[51] High inspiratory airflows are often employed during mechanical ventilation. Such high flows are associated with turbulence, but use of a less dense gas such as helium-oxygen mixture (heliox) makes airflow less turbulent and more laminar. In a pediatric model of mechanical ventilation, albuterol delivery from an MDI was better with a 70/30 heliox than with a 70/30 nitrogen-oxygen mixture.[51] When an MDI was employed in a bench model of adult mechanical ventilation, drug delivery was 50% higher with 80/20 heliox than with oxygen,[30] and drug delivery was inversely correlated with the density of the gas mixture (Fig. 6A). In contrast, nebulizer operation with heliox reduced drug output and respirable mass;[30,52] drug output from the nebulizer was positively correlated with gas density (Fig. 6B). A practical method to maximize pulmonary deposition of nebulizer aerosol in a ventilated patient is to operate the nebulizer with oxygen at a flow rate of 6–8 L/min and to entrain the aerosol into a ventilator circuit contain-ing heliox (Fig. 7).[30] With that method aerosol delivery to the

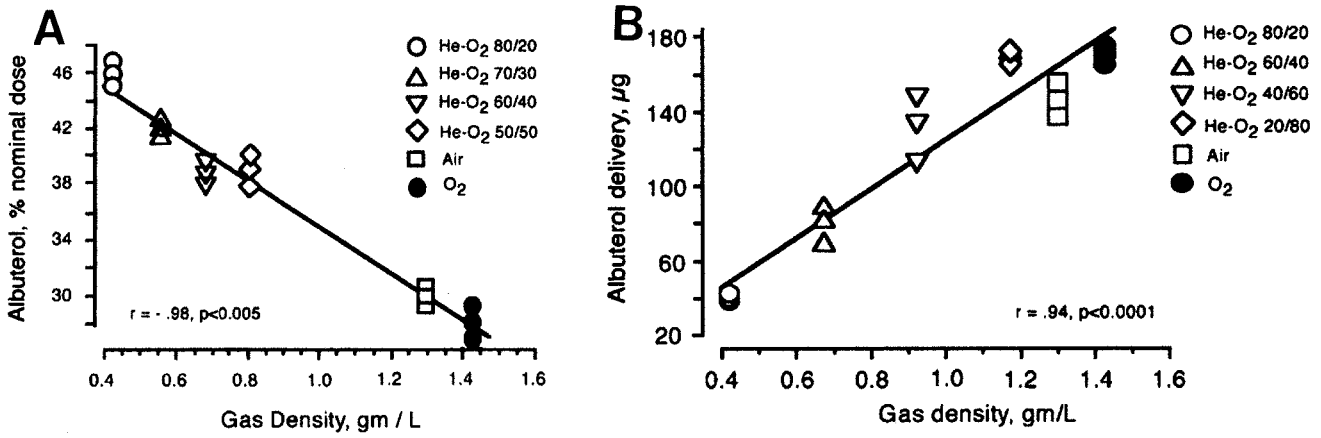

Fig. 6. Effect of gas density on aerosol delivery from a metered-dose inhaler and jet nebulizer. In panel A albuterol was administered via MDI with chamber spacer and an unheated, dry ventilator circuit containing either air, 100% oxygen (O_2), or one of 4 mixtures of helium and oxygen (He-O_2, 80/20, 70/30, 60/40, 50/50%). MDI albuterol delivery (percent of nominal dose) was inversely related ($r = -0.98$, $p < 0.005$) to the density of gas in the ventilator circuit. In panel B albuterol was administered with a jet nebulizer operated at a constant flow of 6 L/min of air, 100% oxygen, or the aforementioned helium-oxygen mixtures. Albuterol output from the nebulizer was positively related ($r = 0.94$, $p < 0.0001$) to the density of gas used to operate the nebulizer. (From Reference 29, with permission).

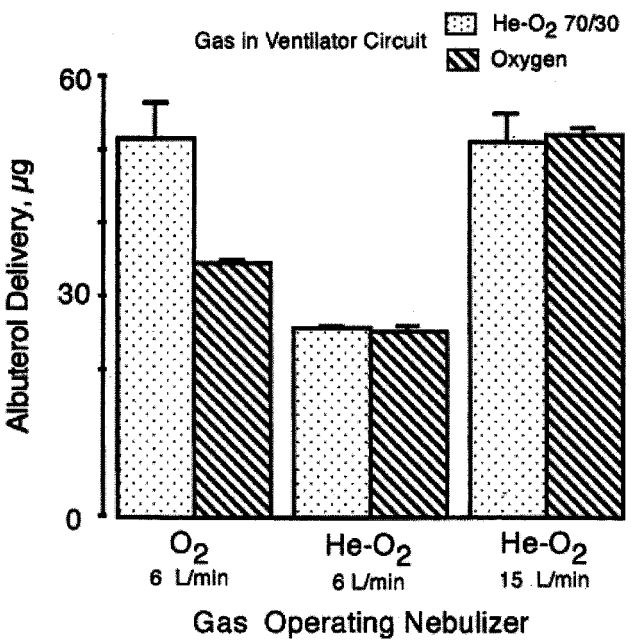

Fig. 7. Effect of gas density and operating flow on aerosol delivery from a nebulizer. A jet nebulizer was operated with 100% oxygen at 6 L/min, with 70/30% helium-oxygen mixture (heliox) at 6 L/min, or with 70/30% heliox at 15 L/min. Drug delivery onto filters was measured with the circuit containing heliox (stippled bars) or oxygen (hatched bars). Albuterol delivery was greatest when the nebulizer was operated with oxygen and the ventilator circuit contained helium-oxygen. The error bars represent standard error of the mean. (From Reference 29, with permission).

lower airways of a tracheobronchial model was 50% higher with helium-oxygen than with oxygen in the ventilator circuit.[30]

Circuit-Related Factors: Artificial Airway. The artificial airway was long believed to be a serious obstacle to effective aerosol delivery during mechanical ventilation. Aerosol impaction in the ETT reduces lower-airway delivery, particularly in pediatric ventilator circuits (ETT inner diameter 3–6 mm).[16,53] However, the efficiency of nebulizer aerosol delivery was similar with ETTs of 7 and 9 mm inner diameter.[20] Earlier investigators overestimated the aerosol delivery impediment created by the artificial airway, probably because the aerosol generator was placed close to the artificial airway. When the aerosol generator is placed at a distance from the ETT instead of being directly connected to it, drug losses in the ETT are minimized and pulmonary deposition is increased.[8] Overall, the type of aerosol generator and the ventilation parameters influence the aerosol deposition more than does the ETT's diameter.[8] Taylor et al[26] attached a long catheter to the nozzle of an MDI and delivered aerosol directly into the trachea (ie, beyond the ETT). Concerns have been raised that, with that delivery system, propellants, surfactant, or other MDI constituents might damage mucosa.[54] Also, the catheter tends to become blocked after only a few MDI actuations.

In Vivo Studies

Several investigators have used radionuclides and measured plasma or urine drug levels to determine pulmonary deposition of aerosols in mechanically ventilated patients.

Radionuclide Studies. Gamma scintigraphy can noninvasively measure total and regional aerosol deposition in the lower respiratory tract. The pulmonary deposition of nebulized aerosol has been variously reported to be 1.22 ±

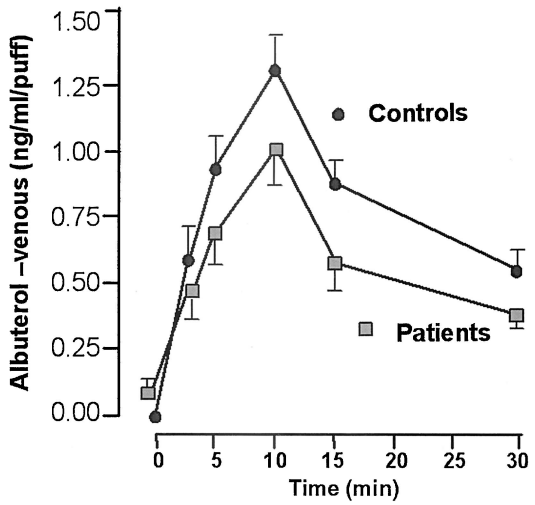

Fig. 8. Comparison of serum albuterol levels in stable, mechanically ventilated patients with chronic obstructive pulmonary disease versus controls (normal volunteers using a metered-dose inhaler [MDI] with holding chamber, with optimal technique). The serum albuterol levels per dose with the MDI were, for the most part, comparable in the mechanically ventilated patients and the control subjects. * $p < 0.05$. (From Reference 57, with permission).

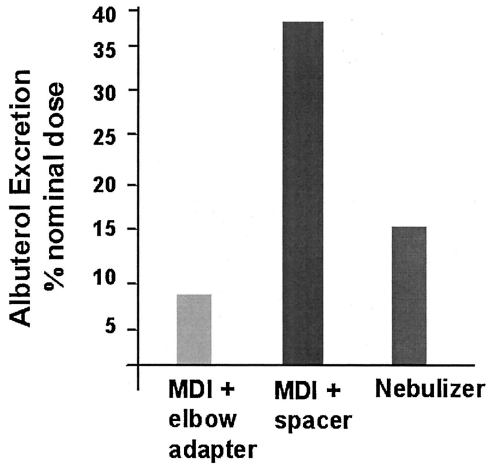

Fig. 9. Comparison of systemic bioavailability of albuterol administered via metered-dose inhaler (MDI) with right-angle elbow adapter, MDI with chamber, or jet nebulizer. Urine was collected for 6 hours after drug administration and measured for amount of albuterol and its sulfate conjugate. The efficiency of the delivery device was determined by the percentage of drug excreted. The drug-delivery efficiency of the 3 systems differed. The MDI with elbow adapter had the lowest efficiency, the jet nebulizer was intermediate, and the MDI with chamber spacer had the highest efficiency. (Data from Reference 58).

0.4%,[6] 2.22 ± 0.8%,[32] 2.9 ± 0.7%,[5] and 15.3 ± 9.5%.[15] Those differences may be attributable to differences in the type of radiolabel used, types of nebulizer employed, treatment time, humidification, and the methods used to calculate the amount of aerosol deposited.[12,15,20] Fuller et al[6,34] actuated an MDI containing fenoterol and technetium[99] pertechnate into a cylindrical chamber placed in the inspiratory limb. About 6% of the dose was deposited in the lower respiratory tract—a value significantly lower than that reported with an MDI-with-spacer in nonintubated ambulatory patients (10–20%).[55,56]

Pharmacokinetic Studies: Blood and Urine Levels. Unlike nonintubated patients, direct deposition of aerosol in the oropharynx and subsequent enteral absorption cannot occur in intubated patients. Therefore, estimation of plasma levels of drugs administered via MDI should reflect lower-respiratory-tract deposition, even though the site of aerosol deposition cannot be determined. Very low plasma levels of a drug can be accurately estimated using highly sensitive assays.[57] In the report by Duarte et al, administration of albuterol via MDI-with-spacer to mechanically ventilated patients produced peak serum levels similar to those in healthy control subjects (Fig. 8),[57] although the area under the concentration-time curve was lower for the patients than for the controls. Those findings, together with the corrected figures from radionuclide studies, have verified the somewhat decreased efficiency of aerosol deposition in the lower respiratory tract of mechanically ventilated patients. Nevertheless, satisfactory deposition can be obtained when the administration technique is carefully regulated.

Estimation of urine levels is another noninvasive method for assessing overall bioavailability of a drug after its administration, though the techniques for measuring urine albuterol level are not as sensitive as those for measuring plasma levels. Marik et al measured urinary albuterol excretion in 30 mechanically ventilated patients who had normal renal function.[58] They found that albuterol recovery in the urine was significantly influenced by the drug administration technique. The highest recovery of albuterol (38%) occurred after administration via MDI-with-spacer. Nebulizer administration was associated with 16% recovery. Administration via MDI with right-angle port connected to the ETT was associated with 9% recovery (Fig. 9).[58] These results corroborated previous investigations that found very low efficiency of drug delivery with the adapter connected to the ETT.[27,28,34]

Reconciling In Vitro Estimates of Drug Delivery With In Vivo Estimates of Drug Deposition

Carefully performed in vitro tests with bench models that simulate the clinical situation have played an important role in establishing the scientific basis for inhaled therapy in mechanically ventilated patients. However, there have been marked differences between the in vitro and in vivo estimates of delivery efficiency. Several in vitro model studies of MDI-with-spacer revealed that the dose deliv-

ered to the lower respiratory tract[7,19,27,28] is approximately 5 times the pulmonary deposition estimated by in vivo gamma scintigraphy.[6] The differences between the in vivo and in vitro data may be because of circuit humidity and because the in vitro studies did not account for exhaled aerosol. In a bench model Fink et al[7] found that lower-respiratory-tract delivery of MDI aerosol was 16% with a humidified circuit and 30% with an unhumidified circuit. In mechanically ventilated patients Fink et al found that up to 5% of the aerosol was exhaled.[21] Thus, in vitro studies indicate that approximately 11% (ie, 16% minus 5% exhaled) of an MDI dose deposits in the lower respiratory tract when using a humidified circuit, which is greater than the approximate 6% found in the in vivo studies by Fuller et al.[6] However, the latter in vivo studies did not account for quenching of radioactivity by the tissues of the chest wall,[34] and when a correction is made for that factor, deposition in the lower respiratory tract is approximately 11%.[35] Thus, the deposition values are comparable among those in vitro humidified-circuit studies and the in vivo gamma scintigraphy studies. Moreover, the corrected value for in vivo lower-respiratory-tract deposition in a mechanically ventilated patient with MDI-with-spacer are remarkably close to those observed with the optimal use of an MDI without a spacer (10–14%) in ambulatory patients.[55,56]

There have also been differences between in vitro and gamma scintigraphy measurements of drug delivery from nebulizers.[5,6,15,32] Miller et al correlated in vitro estimates of nebulizer drug delivery with drug deposition observed in vivo during mechanical ventilation[12] and found that circuit humidification and the presence or absence of breath-actuated nebulization accounted for most of the differences. Likewise, those same 2 factors were found to be responsible for most of the differences in antibiotic levels in tracheobronchial aspirates after nebulization of antibiotics to 6 mechanically ventilated patients.[12] There was a good correlation between the in vitro estimates of albuterol delivered via various nebulizers and the antibiotic levels in tracheobronchial aspirates.[12] Thus, in vitro investigations could play an important role in determining the efficiency of various inhalation devices under a variety of conditions encountered during mechanical ventilation.

Administration Techniques

Successful inhalation therapy in mechanically ventilated patients requires careful attention to the administration technique. The optimal techniques are based on consideration of the various factors elucidated above. In clinical practice the technique employed may have to compromise between the optimum operating characteristics of the aerosol device and the patient's clinical condition. For example, a higher duty cycle increases aerosol delivery,[7,15] but it may also worsen dynamic hyperinflation in patients who have airflow limitation. With that caveat in mind Table 3 shows the MDI technique for mechanically ventilated patients and Table 4 shows the nebulizer technique.[57] When those techniques are employed significant lung deposition is achieved[58,59] and a significant response is observed.[35]

Table 3. Optimal Technique for Delivering MDI Aerosol to a Mechanically Ventilated Patient

1. Review order, identify patient, and assess need for bronchodilator
2. Suction endotracheal tube and airway secretions
3. Shake MDI and warm to hand temperature
4. Place MDI in spacer chamber adapter in ventilator circuit
5. Remove HME. Do not disconnect humidifier
6. Coordinate MDI actuation with beginning of inspiration
7. Wait at least 15 s between actuations; administer total dose
8. Monitor for adverse response
9. Reconnect HME
10. Document clinical outcome

MDI = metered-dose inhaler
HME = heat and moisture exchanger
(Adapted from Reference 57)

Aerosol Delivery During Noninvasive Ventilation

Noninvasive positive-pressure ventilation (NPPV) is increasingly being employed to treat acute and chronic respiratory failure. NPPV with a nasal or face mask can often obviate intubation and mechanical ventilation. Pa-

Table 4. Optimal Technique for Delivering Jet Nebulizer Aerosol to a Mechanically Ventilated Patient

1. Review order, identify patient, and assess need for bronchodilator
2. Suction endotracheal tube and airway secretions
3. Place drug in nebulizer to fill volume of 4–6 mL
4. Place nebulizer in the inspiratory line 46 cm from the patient Y-piece
5. Turn off flow-by or continuous flow during nebulizer operation
6. Remove HME from circuit. Do not disconnect humidifier
7. Set gas flow to nebulizer at 6–8 L/min
   a. Use a ventilator if it meets the nebulizer flow requirements and cycles on inspiration, or
   b. Use continuous flow from an external source
8. Adjust ventilator volume limit or pressure limit to compensate for flow added by nebulizer
9. Tap nebulizer periodically until nebulizer begins to sputter
10. Remove nebulizer from circuit, rinse with sterile water, and run dry; store in safe place
11. Reconnect humidifier or HME, return ventilator settings and alarms to previous values
12. Monitor patient for adverse response
13. Assess outcome and document findings

HME = heat and moisture exchanger
(Adapted from Reference 57)

tients with acute or acute-on-chronic respiratory failure who are receiving NPPV often require inhaled bronchodilators for relief of airway obstruction. Chatmongolchart et al[60] used a bench model to determine the ventilator settings and nebulizer position that achieve the maximum aerosol delivery during NPPV. There was a 5-fold variation (5–25% of the nominal dose) in the amount of albuterol delivered via jet nebulizer, depending on the placement of the nebulizer in the circuit, the inspiratory and expiratory positive pressure settings, and the breathing frequency.[60] The highest albuterol delivery (25%) occurred when the nebulizer was placed closer to the patient (between the leak port and the patient connection), the inspiratory pressure was high (20 cm H_2O), and the expiratory pressure was low (5 cm H_2O).[60] The optimum settings to maximize drug delivery with an MDI during NPPV have not been reported as yet but a significant bronchodilator response was observed after MDI albuterol given to stable patients receiving NPPV via mask.[61] Both MDIs and nebulizers could be employed during NPPV but further research is needed to elucidate the optimal techniques for administering inhaled therapy during NPPV.

Summary

A high efficiency of aerosol delivery to the lower respiratory tract is essential for aerosolized drugs to have an optimal effect. In addition, precision and consistency of drug dosing must be achieved to ensure patient safety. The overall therapeutic response is governed by several additional variables, such as the presence and severity of airway disease, presence of mucus, counter-regulatory effects of inflammation and other drugs, and the patient's response. In the intensive care environment patient and clinician safety are paramount considerations. In addition, the overall cost of treatment also deserves recognition. Despite the constraints imposed by the multitude of factors that influence drug delivery efficiency, a better understanding of the scientific basis for aerosol delivery is increasing the potential for using inhaled therapies in mechanically ventilated patients.

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